A PROSPECTIVE PLACEBO CONTROLLED RANDOMIZED CLINICAL STUDY OF TOFACITINIB AS AN ADJUNCT TO CORTICOSTEROIDS IN ACUTE SEVERE ULCERATIVE COLLITIS

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Dedicated

to

Patients suffering

from

Ulcerative Colitis

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Dr. Manjeet Kumar Goyal

LIST OF ABBREVIATIONS

1. 5-ASA - 5-Amino Salicylic Acid
2. AE- Adverse Effect
3. ASUC- Acute Severe Ulcerative Colitis
4. AZA - Azathioprine
5. BMI - Body Mass Index
6. CD - Crohn’s Disease
7. CDI - Clostridium difficile infection
8. CR- Corticosteroid Resistance
9. CRP- C Reactive Protein
10. CsA- Cyclosporine
11. ER - Endoscopic Remission
12. ESR- Erythrocyte Sedimentation Rate
13. GC- Gluco-Corticoid
14. GCR- Gluco-Corticoid Receptor
15. GI - Gastrointestinal
16. HBsAg - Hepatitis B Surface Antigen
17. HCV - Hepatitis C Virus
18. HIV - Human Immunodeficiency Virus
19. IBD - Inflammatory Bowel Disease
20. IFN- Interferon
21. IFX- Infliximab
22. IL – Interleukin
23. IVCS- Intra-Venous Cortico-Steroids
24. JAK- Janus Kinase

25. M:F - Male: Female
26. NF-Kb - nuclear factor kappa light chain enhancer of activated B cells
27. No. - Number
28. RCT - Randomized control trials
29. SCCAI - Simple Clinical Colitis Activity Index
30. SOC - Standard of care
31. SPSS - Statistical Package for the Social Sciences
32. STAT - Signal Transducers and Activators of Transcription
33. Std - Standard
34. TB- Tuberculosis
35. Th2 - Helper T cells type 2
36. TLR - Toll like receptors
37. TNF-α - Tumour Necrois Factor- α
38. Treg - T- Regulatory
39. TYK- Tyrosine Kinase
40. UC - Ulcerative Colitis

KEY TO MASTER CHART

1.	S.no -	Serial Number
2.	M -	Male
3.	F -	Female
4.	AZA -	Azathioprine
5.	N -	No
6.	Y -	Yes
7.	BMI -	Body mass Index
8.	CRP -	C- Reactive protein
9.	E -	Extent of disease
10.	ER -	Endoscopic Remission
11.	SCCAI -	Simple Clinical Colitis Activity Index

ABSTRACT

Intravenous corticosteroids are the mainstay of treatment of patients hospitalized with acute severe ulcerative colitis (ASUC). However, 30%-40% of the patients are refractory to corticosteroids requiring medical or surgical rescue therapy. The present placebo controlled randomized trial was performed to determine if addition of tofacitinib to corticosteroids was superior to corticosteroids alone in patients hospitalized with ASUC

Methods: This was a single centre, double blind, randomized, controlled trial conducted at Dayanand Medical College and Hospital, Ludhiana, India from 1st October 2021- 31st December 2022. Eligible adult patients with ASUC (defined by Truelove and Witts severity criteria) were randomly assigned to receive either tofacitinib (10 mg thrice daily) or a matching placebo for 7 days. Intravenous corticosteroids (hydrocortisone 100 mg q6h) were continued in both the arms. The primary end point was response to treatment (as per Travis criteria) at days 3 and 7 of the treatment. The key secondary outcome was the proportion of patients in clinical remission and proportion of patients requiring initiation of infliximab/cyclosporine or undergoing colectomy and within 8 weeks following randomization.

Results: Between October 2021 and December 2022, 104 patients were enrolled and randomly assigned to a treatment group (53 to tofacitinib and 51 to placebo). A total of 42(79.25%) out of 53 patients who received tofacitinib whereas 30 (58.82%) out of 51 patients responded as per Travis criteria in placebo arm (p=0.024). Similarly, 44(83.02%) out of 53 patients of tofacitinib arm responded to treatment whereas 31 (60.78%) out of 51 patients responded in pacebo group, on day 7. The colectomy free survival of tofacitinib arm (88.68%) was significantly high in comparison to placebo arm (72.55%) (p=0.037) 1 patient died in tofacitinib group when compared to 4 deaths in pacebo arm. Most of the treatment related adverse effects were mild. One patient, receiving tofacitinib, developed seizures secondary to haemorrhagic venous infarct in the left temporal lobe along with dural venous sinus thrombosis.

Conclusion: Tofacitinib as an add-on therapy to corticosteroids in acute severe ulcerative colitis improved treatment responsiveness and decreased the need for medical or surgical rescue therapy.

Keywords: Ulcerative colitis, tofacitinib, colectomy-free survival

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INTRODUCTION

Ulcerative Colitis (UC) is a chronic relapsing and remitting immune-mediated inflammatory condition of the large intestine that is associated with inflammation of the rectum but often extends proximally to involve additional areas of the colon. [1] UC was first described by Samuel Wilks in '*Morbid appearances in the intestine of Miss Bankes'* in 1859; but the exact pathogenesis is yet to be delineated. [2]

UC has a bimodal age of distribution with first peak in second to fourth decade of life and the other in sixth to seventh decade of life.[3] The incidence of UC is on the rise worldwide with annual incidence ranging from 8.8 to 23.1 per 100,000 person-years in North America, 0.6 to 24.3 per 100,000 person-years in Europe, and 7.3 to 17.4 in Oceania. [4] Interestingly, in the twenty-first century, studies have found that the incidence of UC in developed nations has stabilized and, in some cases, even declined whereas its incidence in developing countries has been on the rise with annual prevalence between 2.0 and 6.0 per 100,000 individuals in India.[1, 5] Moreover, there is a staggering rise in both the disease burden and the population India is projected to have amongst the highest numbers of IBD patients in the world. IBD affects individuals in their most productive years and is associated with a considerable morbidity and loss of functional capacity along with the burden of costly and prolonged treatment, the lack of medical insurance cover, and the poor acceptance of patients for surgery.

Ulcerative colitis, a disease with a relapsing and remitting course, usually tends to have a mild to moderate disease course. However, 15-25% of patients with UC will experience at least one episode of severe flare and almost 10–20% will present with acute severe ulcerative colitis (ASUC) at the time of diagnosis. [6–8] ASUC is a debilitating condition and requires prompt hospitalization and intensive care. Its diagnosis is based on the Truelove and Witts criteria, which combines frequency of bloody stools (⩾6 per day) with at least one marker of systemic toxicity: pulse rate >90

bpm, temperature >37.8°C, hemoglobin <10.5 g/dl and/or an ESR >30 mm/h.[9]

Intravenous steroids are the mainstay of therapy for ASUC, but 30–40% of patients will fail to respond to steroids and require progression to second-line therapy [infliximab (IFX) or cyclosporine (CsA)]. [10] However, the second line drugs are associated with a significant risk of adverse events. ASUC may require colectomy in 20% of cases on the first admission and in 40% of cases after two admissions. [6] Colectomy carries a 5% postoperative mortality risk when done emergently in the hospital setting. [11–13] Moreover, there remains a 1% mortality associated with severe flares of UC. [14] Infliximab and cyclosporine increases the risk of opportunistic infections and reactivation of latent tuberculosis (TB). [10] Therefore, in TB endemic countries like India with limited resources, widespread use of these drugs is restricted. High cost of therapy also limits their use. It is thus important to explore new treatment modalities for ASUC to improve steroid responsiveness that results in a decreased need for rescue therapy.

Tofacitinib, a JAK-STAT (Janus kinase-signal transducers and activators of transcription) inhibitor and an anti-inflammatory drug, is approved for treatment of moderate UC. [15] JAKs are intracellular tyrosine kinases which mediate the signal transduction of various cytokines, like IL-6, IL-7, Il-10, IL-12, IFNα, IFNβ 2, 4, 7, 9 etc. [16] The advantages of JAK-STAT inhibitors over monoclonal antibodies include, the oral administration, predictable pharmacokinetics with reduced plasma half-life, rapid onset of action, quick clearance, lack of immunogenicity and an intracellular target. [17] Additionally, tofacitinib has a broader spectrum whereas biologics are generally selective for a cytokine or integrin. [18]

Tofacitinib has recently been used as second line treatment after steroid failure in previous infliximab failures or third line after sequential steroid and infliximab or cyclosporine failure and showed high short term colectomy free survival among refractory patients. The present study was

planned to use tofacitinib upfront in ASUC as an adjunct to corticosteroid and evaluate its efficacy on treatment responsiveness. We hypothesized that addition of tofacitinib to corticosteroids will increase the responsiveness in ASUC. Therefore, the current study was planned to evaluate the efficacy of tofacitinib as an adjunct to corticosteroids in the management of ASUC and its impact on treatment responsiveness. This will be a randomized placebo controlled study where the patients will be randomized into two groups with one group receiving tofacitinib along with corticosteroids whereas other group will receive placebo plus corticosteroids.

AIMS & OBJECTIVES

Primary Objective

- To compare the efficacy of tofacitinib used as an adjunct to corticosteroids versus corticosteroids alone in inducing treatment response among patients with acute severe ulcerative colitis.

Secondary Objective

- To compare the rates of rescue medical therapy and colectomy in the two groups at week 8 of randomization.

REVIEW OF LITERATURE

The first case of UC was reported by Matthew Baillie in 1793 as an unknown deadly bowel disease. [19] *However, it was in 1859 when* Sir Samuel Wilks described Inflammatory Bowel Disease (IBD) as 'idiopathic colitis' and recognized it to be distinct from the then much more common bacillary dysentery. He also reported the pathological finding of a dilated and thinned colon with severe pan-colonic inflammation which is now recognized as toxic megacolon. [19]

Dr. Wilks introduced the term "UC" into the medical vernacular in 1875. [20] A disease that was not recognized a generation earlier now was now emerging in epidemic proportions. In 1909, the Royal Society of Medicine held a symposium to review hundreds of cases of UC hospitalized in London, England. Sir William Allchin addressed the symposium, stating, "UC is a provisional title and its future retention or rejection will be determined by a clearing up of certain points in connection with the natural history of the disease." [21] The incidence of UC rose rapidly in North America and Europe throughout the first few decades of the 1900s. [21] In the early 20th century, inflammation of the ileum challenged the notion of isolated colonic involvement in UC. [21]

Ulcerative Colitis (UC) is a chronic relapsing and remitting immune-mediated inflammatory condition of the large intestine that is associated with inflammation of the rectum but often extends proximally to involve additional areas of the colon. [1] The complex interplay of genetic predisposition, environmental factors, epithelial barrier defects, dysregulated immune responses, microbiological factors and environmental factors are hypothesized to play a key role in disease pathogenesis. Exposure to such factors leads to inappropriate immune responses against enteric commensal microbes in a genetically susceptible individuals.[22, 23]

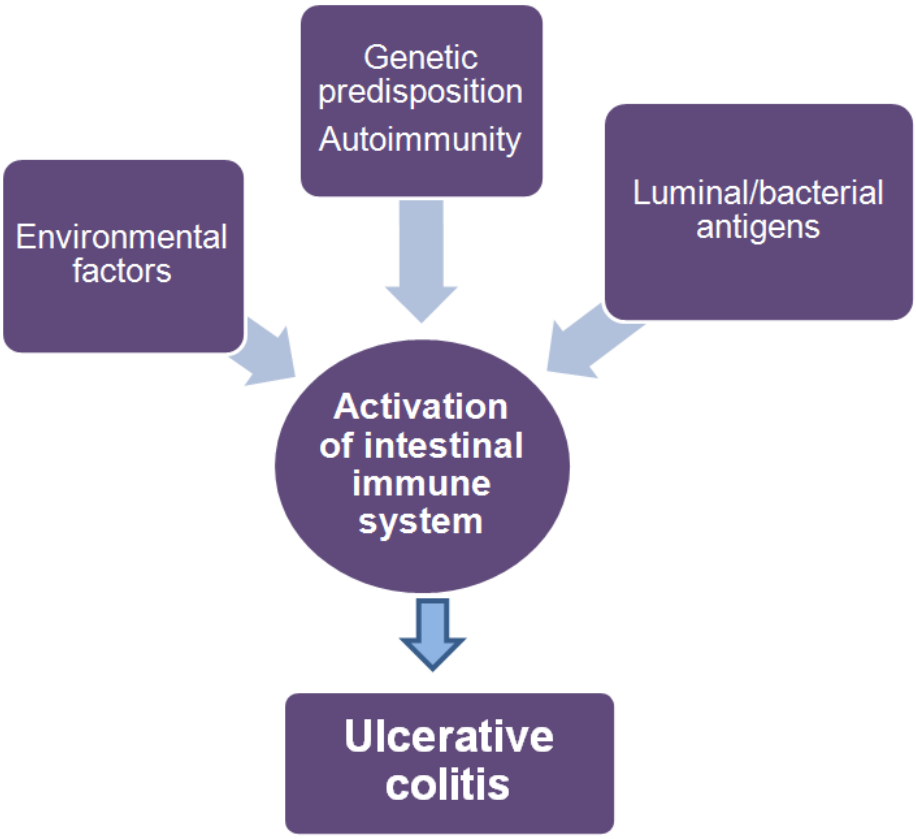

Figure1: Pathogenesis of Ulcerative Colitis [22, 23]

Ulcerative Colitis in India

Inflammatory bowel disease (IBD) has been considered a disease of white people of European descent living in industrialized regions of the Western world. However, over the last two decades, India appears to be at the epidemiologic crossroads where infectious diseases as well as diseases hitherto considered to be diseases of the Western world are being witnessed.[24] Although the rarity of IBD in India has been questioned more than 50 years back, the lack of good epidemiological studies could not reconfirm this astute observation. [25] The study of IBD epidemiology in these regions has been hampered by several factors including a lack of universal accessibility to health care and no hospital-based studies along with the absence of standardized case definitions, relevant databases, registries with appropriate validation and prospective data collection. The

first such study was conducted by Khosla et al. in 1984 in Haryana in North India and the other one was conducted 15 years later by Sood et al. in Punjab. [26, 27] This is the only population based study from India to estimate the prevalence and incidence of ulcerative colitis. A house to house survey was conducted and patients with diarrhea were considered as suspected cases and they subsequently underwent sigmoidoscopy or colonoscopy along with rectal biopsy and diagnosis of ulcerative colitis was made. The computed age-standardized prevalence of UC was 44.3/100,000 with incidence reported to be 6.02/100,000. [26]

It has been noticed that the IBD burden in India is highest among the other Asian countries with the estimated affected population being the second highest in the world after the United States. [24, 28] The plausible explanation for such observation is greater urbanization that exposes populations to considerably different environmental factors for example, pollutants and lifestyle changes. [28] In addition to this, westernization has led to significant lifestyle changes including changes in dietary patterns that lead to changes in the host microbiome as well as adaptive immunity. [29]

Thus, it can be safely concluded that IBD can no longer be considered in its infancy in India; and with a staggering rise in both the disease burden and the population, India is projected to have the highest numbers of IBD patients in the world. It affects individuals in their most productive years and results in considerable morbidity and loss of functional capacity along with the burden of costly and prolonged treatment. UC in India is as aggressive as in the West and requires a similar treatment approach with additional challenges like the expense of therapy, the lack of medical insurance coverage, and the poor acceptance of patients for surgery. [30]

Classification of Ulcerative Colitis (UC)

There are various classification scales proposed in the literature for the classification of UC over the years but modified Truelove and Witt's criteria is the most widely used and accepted worldwide to classify patients into

various categories (mild, moderate and severe) on the basis of their stool frequency and various clinical and biochemical markers of inflammation.

Modified Truelove and Witt's Criteria

Dr. Truelove and Witts in 1955 published an article on "cortisone in ulcerative colitis" proposed diagnostic criteria to define acute severe ulcerative colitis. [9] A patient is diagnosed with acute sever ulcerative colitis, if there are ≥6 stools with blood with 1 or more features of systemic toxicity (hemoglobin <10.5g/dL, pulse > 90bpm, temperature > 37.8 degree Celsius and raised inflammatory markers [ESR/CRP]). [31] However, as hemoglobin is low in developing countries like India, Saransh jain et al conducted a study in 2018 to evaluate the relevance of the criteria for Indian population. [32] They concluded that all the patients met the criteria for ASUC even after excluding hemoglobin as an additional criterion from the Truelove and Witts criteria thus confirmed its relevance in Indian settings. [32]

Parameter	Mild	Moderate	Severe
Bloody stool/day	<4	≥4 or more if	≥6 and
Pulse	<90 bpm	≤90 bpm	> 90 bpm or
Temperature	<37.5 C	≤ 37.8 C	> 37.8 C or
Haemoglobin	>11.5 g/dL	>10.5 g/dL	<10.5 g/dL
ESR or	<20 mm/h	≤ 30 mm/h	>30 mm/h or
CRP	normal	≤ 30 mg/l	>30 mg/l

Table 1: Modified Truelove and Witts Criteria [31]

Montreal Classification

In 2006, Montreal working group classified UC on the basis of extent of colonic involvement on endoscopy into three subgroups (table 2). The sub-classification was found to have clear biological relevance in terms of

the response of patients to medical therapy (differential response to topical therapy), and also with respect to rates of medication usage, hospitalisation, colorectal malignancy or colectomy. Furthermore, various studies have shown association of specific serological and genetic markers with extensive ulcerative colitis, making this subset of particular importance to study the patho-physiology. [33, 34] The major drawback of the extent based classification system is instability of disease extent over time, underlining the dynamic nature of inflammatory bowel disease.

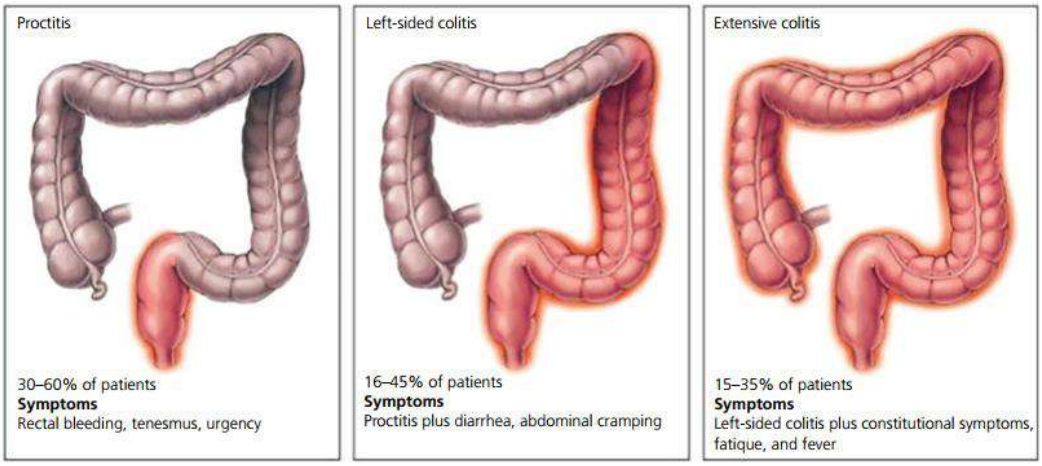

Figure 2: Montreal Classification of Ulcerative Colitis[35]

Extent	Anatomy
E1 Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2 Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3 Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

Table 2: Montreal Classification For Extent Of Ulcerative Colitis [35]

Acute Severe Ulcerative Colitis (ASUC)

ASUC is a potentially life-threatening medical emergency that requires prompt recognition and early initiation of treatment. It is associated with significant morbidity and has a mortality rate of approximately 1%. [36] Overall, 15–25% of patients with ulcerative colitis develop an acute severe flare necessitating hospitalization during the course of their disease, often at the time of disease onset. [37] It is associated with significant morbidity and has a mortality rate of approximately 1%. [36] The in-patient mortality rate of ASUC in patients aged 60 years or more is approximately 4% in patients aged 60 or more whereas it is less than 1% in younger patients. [38] It is noteworthy to mention that about 20% of patients with UC will develop an episode of ASUC and 15-25% will have a severe exacerbation that will require admission at some point. [7, 39] ASUC is most easily defined by the Truelove and Witts criteria (TABLE 1). [9] It can lead to several complications such as toxic megacolon, perforation, uncontrolled bleeding, etc. as well as the potential need for colectomy. The rate of colectomy after an ASUC episode (urgent or elective) historically ranges between 20 and 30%, with a mortality rate of 5% associated with urgent procedure. The colectomy rate can be as high as 38.2% in those requiring multiple admissions. [6] In the biologic era, the reported colectomy rates after admission for ASUC have varied from 19 to 23%. [40, 41] Another study that prospectively evaluated a cohort of 423 patients with newly diagnosed UC and followed them for 10 years reported a cumulative colectomy rate of 9.8%. [40] Interestingly, a study compared colectomy rates between 1997 and 2009 stratifying the procedure by elective or emergent reported and has shown that the elective and urgent colectomy rates have decreased by 7.4% and 1.4%, respectively over the time period studied. [42]

Management of Acute Severe Ulcerative Colitis

Corticosteroids

Intra-venous Cortico-Steroids (IVCS) are the main stay of ASUC treatment. Corticosteroids down regulate pro-inflammatory cytokines such as TNF, IL-6, etc. by inhibiting NFκB activation. [43] There is no study that has compared the efficacy of different doses of intravenous hydrocortisone and methylprednisolone in ASUC. However, a meta-regression analysis indicated no incremental benefit for using doses of methylprednisolone beyond 60 mg in terms of reduction of colectomy rates. [44-46]

Since the seminal observation by Truelove and Witts 60 years ago, corticosteroids remain the cornerstone of therapy for ASUC. [9] In their pivotal study, 213 patients were randomly allocated to receive 100 mg of cortisone or placebo for a period of 6 weeks. Higher rates of clinical remission was observed in the steroid-treated group than the placebo group (41% versus 16%), along with a large reduction in mortality (24% versus 7%). Furthermore, improvements in sigmoidoscopic appearance were seen more frequently in the cortisone-treated patients than the placebo group. [9] Later on, Truelove and Jewell in 1974 published the results of a trial which enrolled 49 patients with severe exacerbations of ulcerative colitis who were treated with 5 days of intravenous methylprednisolone. [47] The results were significant with 73% achieving remission. [47]

Later, a systematic review and meta-regression of cohort studies and RCTs including 1991 patients from 32 trials of steroid therapy for ASUC between the years 1974 and 2006, reported the overall response to steroids (including intravenous hydrocortisone, methylprednisolone and betamethasone) of 67% and demonstrated a reduction of mortality associated with ASUC. [14] One-third of patients (27%) underwent colectomy during the index hospitalization. However, meta-regression revealed no benefit to a dose higher than 60 mg of methylprednisolone. [14]

Response to IVCS is usually apparent within 3–5 days of initiation, and additional response after 7 days is unlikely. Extending treatment beyond 7–10 days seems to confer no additional benefits. [14]

Most patients hospitalized with ASUC should continue to receive enteral diet, however gluten can be avoided in certain cases as RCTs have demonstrated no additional benefit with bowel rest; only patients with toxic colitis or megacolon should be made nil-per-os because of the potential for imminent surgical intervention. Due to risk of precipitating toxic megacolon, narcotics and antidiarrheal agents should be avoided.

ASUC is a hypercoagulable state, with increased risk of venous and arterial thromboembolic events. Inflammatory bowel disease is associated with an increased risk of VTE. [48] This risk is particularly apparent in hospitalized patients and is proportional to severity of inflammation. [48] Other factors contributing to VTE risk in these patients include loss of antithrombotic proteins, use of corticosteroids, reduced mobility, and abdominal surgery. [49] As many patients with IBD who develop VTE do not seem to have an underlying genetic predisposition or other risk factors, thromboprophylaxis with low-molecular-weight heparin should be given to all hospitalized patients with ASUC. [50] It is also noteworthy that empiric antibiotics in the absence of infection are not recommended in patients with ASUC, though they can be considered in patients with toxic megacolon at imminent risk of perforation. [50]

Burden of corticosteroid resistance in Acute Severe Ulcerative Colitis

Intravenous glucocorticoids have been considered the first-line management for acute severe UC for almost 50 years, but 30–40% of hospitalized patients are refractory to this treatment. [51] In a pioneer study conducted by Truelove et al, they found that out of 49 patients of ASUC treated with IV corticosteroids, one-third had no response by day 5. [47] Turner et al conducted a systemic review and meta-regression analysis in 2006 which included 32 studies on ASUC between 1974-2006 and

concluded that 30.4% failed to respond to corticosteroids. [14] Similarly, Festa et al observed that out of 372 patients, approximately 40 % were refractory and required rescue therapy in the form of Infliximab, cyclosporine or colectomy. [52]

Trial	Number of patients	Remission rate (%)	Partial response (%)	Colectomy/failure rate (%)
Truelove and Witts [9]	109	41.3	27.5	31.2
Truelove et al [47]	87	60	15	25
Chakravarty [53]	89	72	---	28
Travis et al. [54]	49	42	31	27
Lindgren et al [55]	97	40	26	34

Table3: Rates of steroid resistance in ASUC

In an effort for timely initation of rescue therapy, several predictive indices to identify non-responders to intra-venous corticosteroids have been developed like Oxford or Travis Score, Scottish or Ho index, Lindgren Score, Lichtiger Score, etc. [56] The Oxford or Travis criteria are based on a retrospective case series of 48 patients with ASUC and demonstrated that a stool frequency of >8 or a CRP level of more than 45 mg/l on day 3 of admission was associated with an 85% chance of requiring colectomy during the same admission. [54]

Index	Variables	Diagnostic accuracy
Oxford/ Travis criteria	Stool frequency >8/day; or 3–8/day and CRP >45mg/L	85% chance of requiring colectomy during the same admission
Seo	Stool frequency, hematochezia, nocturnal bowel movements, abdominal pain, and activity level	Negative predictive value 97%; positive predictive value 52%
Scottish/ Ho index	Stool frequency, colonic dilation, hypoalbuminemia	A total of ≥4 points on day 3 is associated with a sensitivity of 85% and specificity of 75% for requirement of colectomy
Swedish	CRP and stool frequency	Positive predictive value ~70%
Lindgren score	Stool frequency per day + 0.14 x CRP (mg/L)	Sensitivity of 78% and specificity of 81% for predicting non-response

Table 4 : Various prognostic score for predicting non-response in ASUC [54, 56]

Mechanism of Corticosteroid Resistance (CR)

Despite advances in new therapies, corticosteroids remain the first-line treatment for moderate to severe UC. However, steroid-refractoriness is a major drawback in the treatment of UC, as it occurs in 40–60% of patients who require rescue therapies. The anti-inflammatory effects of glucocorticoids [GCs] include a variety of biological actions that are highly influenced by many biological and environmental factors.

Glucocorticoid receptor and action

Glucocorticoids (GC) form a complex with the GC receptor [GCR] in the cytoplasm leading to structural modifications which transfers the complex to the cell nucleus by the β-importins. [57] GC-GCR nuclear dimmers then bind to specific DNA regions known as GC response elements [GREs, 5′-GGTACAxxxTGTTCT-3′; x means any base]. Subsequently, the ligand-induced GCR dimers recruit the co-activators and initiate GC-specific gene expression. [58,59] It interferes with NF-κB, AP1 or STAT3-induced gene expression, either by increasing the expression of anti-inflammatory genes such as *ANXA1*, which encodes ANNEXIN-A1, or by transcribing genes such as *TSC22D3*, which block pro-inflammatory gene expression. [60, 61]

Mechanism and molecular basis of glucocorticoid resistance

The molecular mechanisms of glucocorticoid resistance (CR) in UC have been associated with changes in the Glucocorticoid Receptor (GR) isoform levels, polymorphisms in *NR3C1* or genes involved in GC bioavailability, and impaired cytokine production. [62-65]

The GR consists of two isoforms GRα binds to corticosteroids and activates gene transcription whereas GRβ interferes with GR binding to DNA and thus inhibits glucocorticoid action. [66] In 2009, a study was conducted to study the relationship between the expression of GR isoforms and glucocorticoid responsiveness in patients with UC. [63] High levels of the GRα isoform were found in both GC resistant and responsive patients. However, in contrast higher levels of GRβ were seen only in GC

resistant patients when compared with GC responder group. [63] CD4+ and CD8+ T lymphocytes, macrophages and B cells primarily expressed the GRβ receptor in the intestinal mucosa. Other cells involved were, fibroblasts and vascular endothelial cells which expressed GRβ in a minor proportion. These results suggest that a higher ratio of GRβ/GRα in inflammatory mononuclear cells disturbs the effects of GCs resulting in refractory outcomes.

The other possible predisposing factor to GC resistance in IBD is polymorphisms in GR protein-encoding NR3C gene, and ABCD1 (also known as MDR1) gene as well as TNK, FKBP5, MAPK14 and NALP1 genes. [67-68] Single nucleotide polymorphisms (SNPs) in *NR3C1* gene may result in different effects on the receptor structure and its signal transduction leading to altered glucocorticoid responsiveness in IBD patients. [62] The most studied SNPs that could induce a refractory phenotype in IBDs patients are: ER22/23EK (rs6189 and rs6190), N363S (rs6195), and BcII (rs41423247). [62] Among these, ER22/23EK polymorphisms result in decreased transactivation capacity of GR and thus are associated with glucocorticoid resistance. [69]

Polymorphisms in the *MDR1* gene encoding for the P glycoprotein (Pgp) are also well studied in the context of glucocorticoid responsiveness. Pgp is a trans-membrane glycoprotein responsible for the absorption, distribution, metabolism and excretion of various drugs including GC. Therefore, polymorphisms in the *MDR1* gene have a major impact on the therapeutic efficacy of the glucocorticoids as these lead to variation in expression levels and the activity of MDR1 encoded Pgp. [70] Additionally, higher expression of pro-inflammatory cytokines like IL-6 and IL-8 has also been associated with GC resistance. [71] A similar correlation between the IL-6 and GC unresponsiveness was found in a study involving 79 pediatric patients with ASUC on IVCS treatment. In higher levels of IL6 were found in patients who did not respond to GC when compared with responders. [72] However this correlation could reflect a

cause-effect relationship between the signaling of the GC receptor and the expression of pro-inflammatory cytokines given the pleiotropic nature of IL-6. Although the real reason for the failure to response remains unclear. [73]

The JAK-STAT signaling physiology

The JAK-STAT pathway mediates signal transduction from cell-membrane receptors to the nucleus via interaction between the receptor, the ligand, Janus Kinases (JAKs) and the signal transducer and activators of transcription (STATs) (Figure 3) JAKs were discovered in the 1990s and are family of four intracellular non-receptor tyrosine protein kinases namely JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). [74] On the other hand the human STAT family contains seven STATs: STAT 1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6. [74] There are four receptor families that use the JAK/STAT pathway: the common γ-chain receptor family, the common β-chain receptor family, the common glycoprotein-130 (gp130) receptor family, and the type II receptor family (Table 5). [74] The JAK/STAT pathway is essential for wide range of cytokines and growth factors, leading to critical cellular events like cell growth, cell survival, differentiation and migration. [75]

RECEPTOR FAMILY	CYTOKINE	ACTIVATION	FUNCTION
Common γ-chain receptor family	IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21	JAK1/JAK3	Modulates the adaptive immune function, including B-cell maturation and Th1, Th2 and Th17 differentiation.
Common β-chain receptor	IL 3 and IL 5	JAK 2	Erythropoiesis, myelopoiesis, and platelet production
Common glycoprotein-130 family	IL 6, Il 11, Il-12 and IL-23	JAK1 and JAK2/TYK2	Regulate innate immune responses and Th1, Th2 and Th17 differentiation and production of pro-inflammatory cytokines.
Type II	IFN-γ	JAK1/JAK2 and TYK2	Regulates the intestinal response against bacterial pathogens

Table 5 : Janus kinases and signaling pathways [76]

Once, cytokine binds to its receptor, JAKs transmit signals to the nucleus through a series of sequential steps (figure 3). [77]

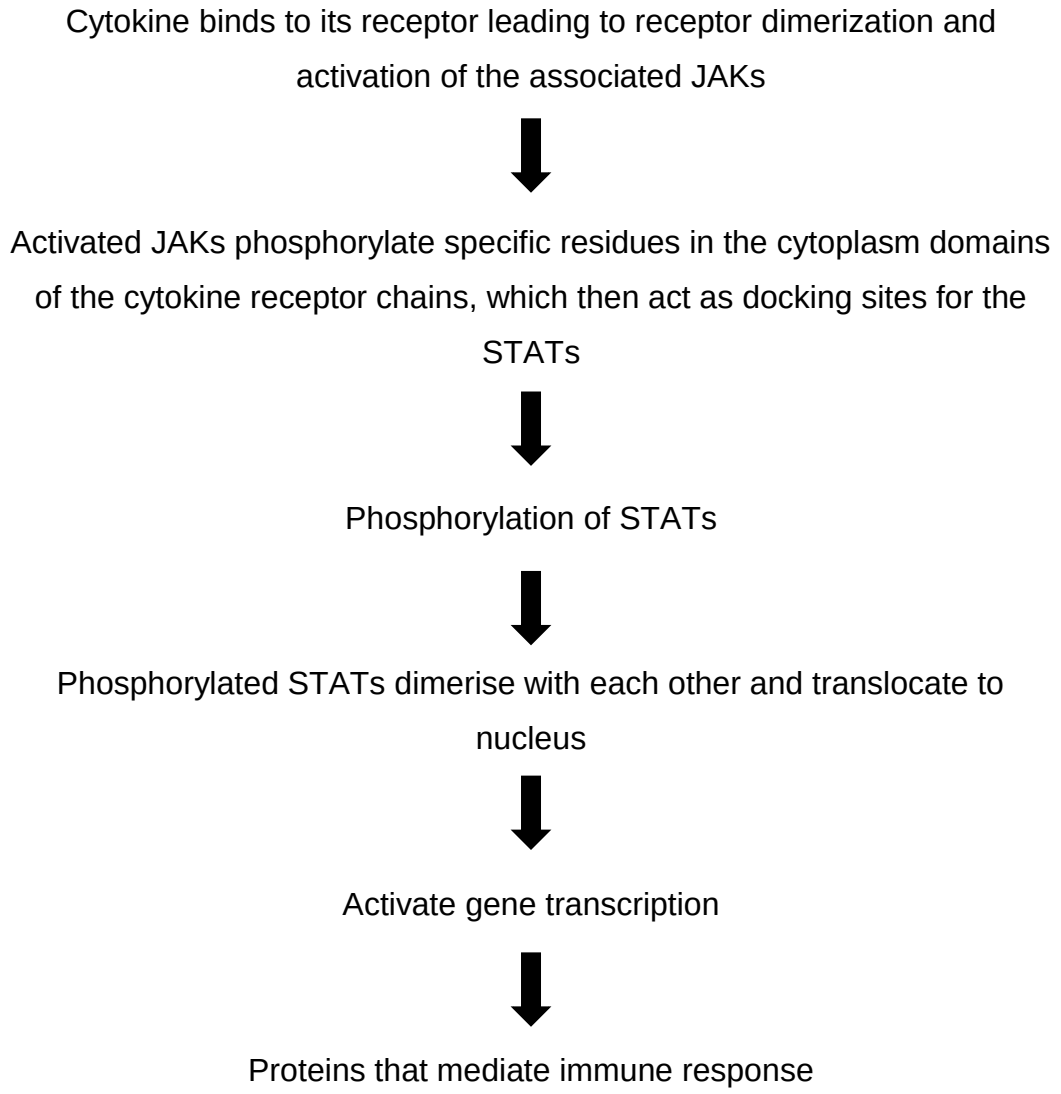
Cytokine binds to its receptor leading to receptor dimerization and activation of the associated JAKs
Activated JAKs phosphorylate specific residues in the cytoplasm domains of the cytokine receptor chains, which then act as docking sites for the STATs
Phosphorylation of STATs
Phosphorylated STATs dimerise with each other and translocate to nucleus
Activate gene transcription
Proteins that mediate immune response

Figure 3: JAK-STAT Pathway [77]

JAK-STAT signaling in the pathogenesis of Ulcerative Colitis

The pathogenesis of UC is multifactorial, resulting from an abnormal immune response to components of the microbiome in genetically susceptible individuals exposed to triggering environmental factors. [78] Cytokines are soluble low-molecular-weight proteins or glycoproteins involved in the regulation of several biological activities in the immune system. It is noteworthy that cytokines usually exert their biological functions through interaction with trans membrane receptors and subsequent activation of JAK and signal transducers and activators of transcription (STAT). [74] A blockade of JAKs-mediated inflammatory pathways may result in modulation of the adaptive and innate immune responses involved in IBD pathogenesis and may, therefore, be effective in interrupting the chronic cycle of gastrointestinal inflammation.

The main cytokines participating in immune activation in UC are: TNF-alpha, IL-6, IL-1beta, IL-5, IL-13, IL-17, IL- 18, IL-8, IL-33, TL1A, IL-12 and IL-23. [79, 80] The IL-6 receptor signals preferably through JAK1, JAK 2 and TYK2 which activates STAT3 and stimulates the proliferation of Th-17 cells leading to recruitment and activation of macrophages and neutrophils in the lamina propria. [81] Similarly, IL-12 and IL-23 signaling through JAK1 and TYK2 promotes activation of Th1 cells and Th17 respectively. [82] IL13 also promotes fibrosis and induces apoptosis in intestinal epithelial cells through JAK-STAT pathway. [83, 84] IL-23 signals through a dimeric receptor and activates JAK2 and TYK2 firstly and then STAT3 and STAT4 leading to an inflammatory response. [85] Therefore, JAK-STAT pathway holds an important place in the pathogenesis of multifactorial immune-related pathogenesis of UC and drugs targeting JAK-STAT pathway can be used in the management of UC.

Tofacitinib in Ulcerative Colitis

The better understanding and characterization of JAK-STAT pathway in the pathogenesis of UC has paved the way to develop small molecule inhibitors for the treatment of immune-mediated inflammatory diseases,

including UC. [86] Tofacitinib (CP-690550) is a JAK inhibitor currently approved by Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of moderately severe UC patients. [54] It is similar in structure to ATP and thus competes with ATP for binding to the active site of the kinase domain of the receptor. As a result, the drug inhibits the phosphorylation and activation of JAK, thereby preventing the phosphorylation and activation of STATs, and hence the activation of gene transcription. [87] This leads to decreased cytokine production as well as the modulation of immune response. [88] Although, tofacitinib is a pan-JAK inhibitor, it targets JAK1 and JAK3 with a higher specificity than JAK2 and TYK2. [86]

Tofacitinib has been used in the management of rheumatoid arthritis for the last many years; however, it has been studied and approved for moderate-severe ulcerative colitis (UC) cases in the last couple of years. The phase 3 clinical trials for induction therapy, OCTAVE induction (1 and 2) have demonstrated significantly higher rates of remission, mucosal healing and improvement in health-related quality of life in tofacitinib treatment arms as compared to placebo. [15] The maintenance treatment study, OCTAVE Sustain, also showed that the treatment end-points were maintained at 52 weeks with tofacitinib as compared to placebo. [89] Subsequently, post hoc analysis of phase III clinical studies have shown that the efficacy and safety of tofacitinib among East Asian population (Japan, Korea, Taiwan) is comparable to the global analysis. [90] In a real-world cohort, clinical remission was achieved among 33% patients of moderately severe active UC patients who had failed treatment with two classes of biologic therapies. After one year, 42% of patients remained in steroid-free clinical remission. [91,92]

As demonstrated in OCTAVE, the efficacy increases with higher tofacitinib doses. But as adverse events (AEs) are also dose-dependent, the guidelines advocate the use of the lowest effective dose to maintain response where possible. OCTAVE Open data, on the other hand,

supports the effectiveness of a dose-escalating strategy to recapture response in patients losing response on 5 mg BD maintenance. [92]

In the OCTAVE studies, during the maintenance phase of the trial, the most commonly reported AEs in any treatment group were nasopharyngitis, arthralgia and headache. In the OCTAVE (1 and 2) and OCTAVE Sustain, similar proportions of patients across treatment groups had adverse events. However, the incidence of herpes zoster in the OCTAVE sustain trial was found to be higher in the patients treated with tofacitinib 10 mg (5.1%) and 5 mg (1.5%) as compared to the placebo group (0.5%). However, none of the cases of herpes zoster seen were classed as severe AEs and treatment did not need to be discontinued. The results of the open-label long-term extension study from the OCTAVE Sustain, shows a higher proportion of patients with abnormal creatinine kinase and lipid levels in the tofacitinib groups as compared to placebo. [93]

Recently, US FDA has issued preliminary results from a safety clinical trial about the increased risk of serious heart-related problems and cancer with tofacitinib (both immediate-release and extended-release preparations) as compared to TNF-α antagonists. [15]

Tofacitinib and Acute Severe Ulcerative Colitis

Tofacitinib has been extensively used in moderately severe ulcerative colitis nowadays. However, data on its use in acute severe ulcerative colitis is sparse. There are several potential advantages associated with its use like oral administration, high potency, rapid onset of action along with rapid clearance [i.e. quick in, quick out], less susceptibility to drug loss related to hypo-albuminaemia, no immunogenicity and treatment effects independent of prior responses to biologics. [94]

The regulatory effects of glucocorticoids are mediated through modulation of transcription factors and cytokine production. Combination of IL-2 and IL-4 has been shown to promote steroid resistance and more recently it has been shown that IL-2 treatment alone also promotes steroid resistance. [95] IL-2 has also proven to be associated with reduction in

nuclear translocation of the GR. [96] It has been observed that addition of a Janus Kinase inhibitor can effectively block signaling by the IL-2 receptor and can restore steroid sensitivity in previously steroid refractory cases. [97] JAK1 and JAK3 phosphorylate STAT5 following IL-2 binding to its receptor, and it was seen that IL-2 was no longer able to induce steroid resistance. [96] Moreover, T cells from steroid-resistant individuals have been demonstrated to produce more IL-2 than T cells from steroid-sensitive individuals. [97] NF-ĸB is a regulator of cytokine synthesis, and has been shown to have a markedly different distribution in the colon of steroid-resistant individuals with UC. [97] In steroid-resistant patients, activated NF-ĸB was detected predominantly in epithelial cells, whereas in steroid-sensitive subjects, activated NF-ĸB was principally found in macrophages of the lamina propria. [96] It seems reasonable to speculate, therefore, that one mechanism of resistance of lymphocytes to glucocorticoid arises from activation of one or more signalling pathways activated by the IL-2 receptor, and that by inhibiting IL-2 signalling, this resistance may be overcome. [73]

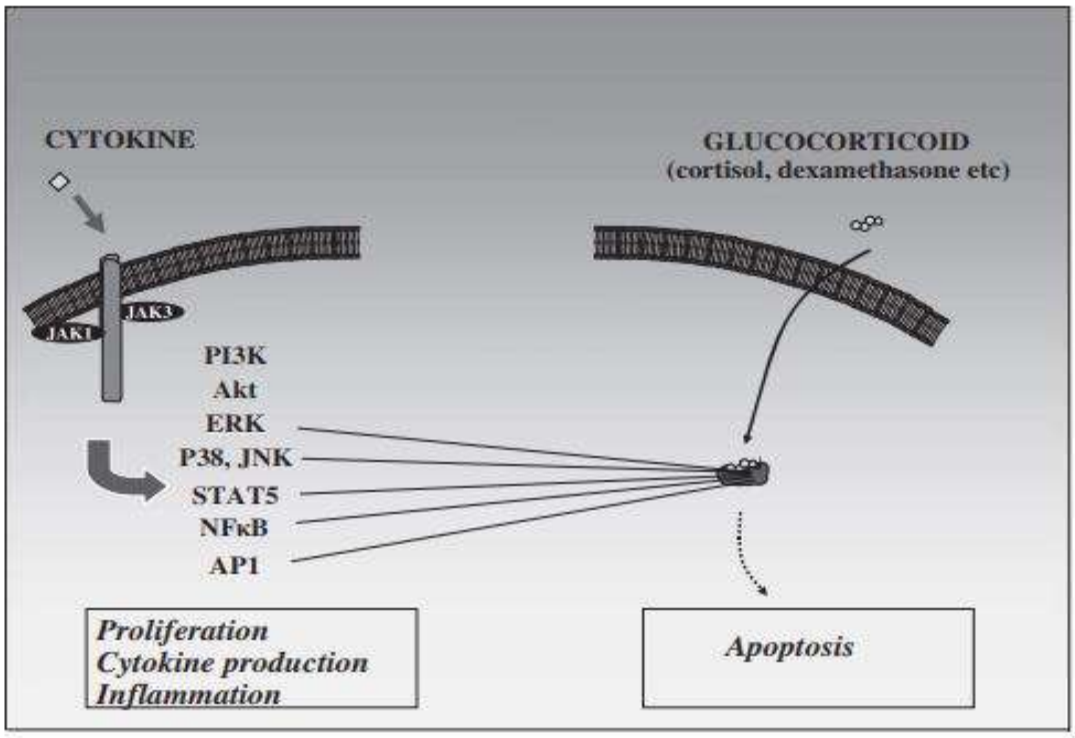

Figure 4: Cytokine signaling, transcription factors and the interface with glucocorticoid signaling. [73]

In a systemic review by Steenholdt et al, 21 studies on the use of tofacitinib in ASUC were included. [98] Total of 148 cases was enrolled where tofacitinib was used as second-line treatment after steroid failure in previous infliximab failures or third-line after sequential steroid and infliximab or cyclosporine failure. The study showed high short term colectomy-free survival among refractory patients who are otherwise deemed to require colectomy with overall colectomy-free survival of 85%at 30 days, 86% at 90-days and 69% at 180-days of follow-up. Clinical remission was seen in 35–69% whereas endoscopic remission was seen in 55% of the cases. Adverse events occurred in 22 patients, predominantly being infectious complications other than herpes zoster [n = 13], and resulted in tofacitinib discontinuation in seven patients. [98] These results, therefore, highlight tofacitinib as promising treatment option for ASUC.

Need for study

Intravenous corticosteroids are the mainstay of therapy for acute severe ulcerative colitis (ASUC), but 30%-40% of patients fail to respond. Tofacitinib has recently been used as second line treatment after steroid failure in previous infliximab failures or third line after sequential steroid and infliximab or cyclosporine failure and showed high short term colectomy free survival among refractory patients but has never been tried upfront alone or albeit in the combination with corticosteroids. The present study was planned to use tofacitinib upfront in ASUC as an adjunct to corticosteroid and evaluate its efficacy on treatment responsiveness. We hypothesized that addition of tofacitinib to corticosteroids will increase the responsiveness in ASUC. Therefore, the current study was planned to evaluate the efficacy of tofacitinib as an adjunct to corticosteroids in the management of ASUC and its impact on treatment responsiveness. This was a randomized placebo controlled study where the patients were randomized into two groups with one group receiving tofacitinib along with corticosteroids whereas other group received placebo plus corticosteorids

MATERIALS AND METHODS

Study design

This was a placebo controlled randomized clinical study in subjects with Acute Severe Ulcerative Colitis (ASUC). The study was conducted on the patients admitted in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India.

Patients/subjects

Adult patients (>18years) with confirmed diagnosis of ulcerative colitis and hospitalized with acute severe UC (defined as 6 or more stools with blood and 1 or more of the following hemoglobin ≤ 10.5 g/dL, erythrocyte sedimentation rate [ESR] ≥30 mm/hr or CRP ≥30 mg/L, fever ≥37.8°C, or tachycardia ≥90/min; the modified Truelove Witts criteria) after obtaining informed consent were enrolled in the study.

Inclusion Criteria

- Patients with acute severe ulcerative colitis (defined by Truelove and
- Witt's Criteria).
- Subject must be at least 18 years of age.
- Subjects willing and able to comply with treatment plan, laboratory tests, daily bowel movement diary call, and other study procedures.
- Subjects willing to provide a written informed consent.

Exclusion Criteria

- Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis.
- Subjects displaying clinical signs of fulminant colitis or toxic megacolon
- Subjects infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses
- Subjects who have been vaccinated with live or attenuated vaccine within 6 weeks of baseline or scheduled to receive these vaccines during study period or within 6 weeks after last dose of study medication

- Subjects with malignancies or a history of malignancies, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin.
- Subjects with current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological disease.
- Pregnant females.

Patients with clinical signs of fulminant colitis, toxic megacolon, or indeterminate, microscopic, ischemic, or infectious colitis, HIV,HBV, HCV infection, administration of live vaccines within 6 months of enrollment or scheduled to receive the vaccines, active or latent tuberculosis, malignancy(current or past), pregnancy or severe renal, hepatic, hematological, metabolic, endocrine, pulmonary, cardiac, neurological disease, etc. restricting the participation in the study were excluded from the study.

Randomization and Treatments

Subjects were randomised using computer-generated randomization schedule to either of the two groups at a 1:1 allocation ratio.

Group 1: Intravenous hydrocortisone (300-400 mg per day in three to four divided doses) plus Tofacitinib (10 mg thrice daily) for 7 days

Group 2: Intravenous hydrocortisone (300-400 mg per day in three to four divided doses) plus Placebo (thrice daily) for 7 days.

In response to intervention, the dose of tofacitinib was decreased to 10 mg twice daily from day 8 onwards and continued till week 8. Intravenous hydrocortisone was shifted to oral prednisolone 40mg/day on day 7 and tapered by 5mg per week as per attending physician’s discretion. Placebo was continued till week 8.

All the enrolled patients continued to receive other standard of care treatment (including intravenous fluids, correction of dyselectrolemia,

enteral nutrition and prophylaxis for deep venous thrombosis) irrespective of the allocation of treatment groups.

Subjects were assigned a subject number in the order of their acceptance into the study. This identifying number was retained throughout the study.

Rescue treatment

Patients who failed to respond to treatment (defined as per Travis criteria; patients with ≥8 stools/day, or 3–8 stools/day with CRP ≥45 mg/L on day 3 and day 7 of the treatment), necessitated initiation of salvage medical therapy (biologics/cyclosporine) or colectomy was started on appropriate treatment at the discretion of the investigator.

Informed Consent

The protocol, informed consent form(s), recruitment materials and all participant materials were submitted for IEC review and approval. Approval of both the protocol and the consent form were obtained before any participant was enrolled. The process of informed consent was initiated prior to the individual agreeing to participate in the study and was continued throughout study participation. Extensive discussion of risks and possible benefits of study participation were provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks was given to the participants. Consent forms were also IEC-approved, and the participant was required to read and review the document or had the document read to him or her. The investigator explained the research study to the participant and answered any questions that arose. The participant signed the informed consent document prior to any study-related assessments or procedures. Participants were given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They could withdraw consent at any time throughout the course of the study.

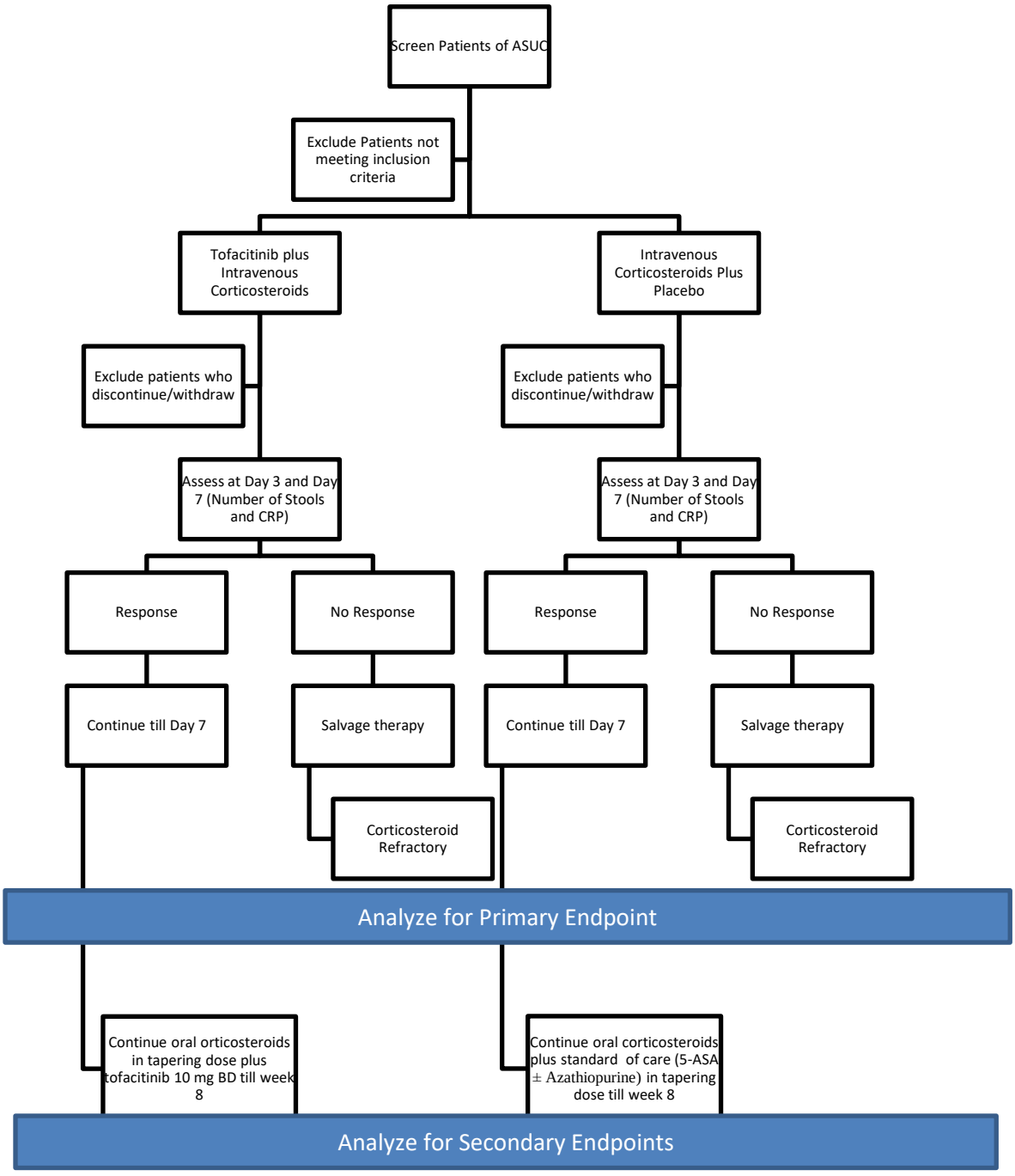
Screen Patients of ASUC
Exclude Patients not meeting inclusion criteria
Tofacitinib plus Intravenous Corticosteroids
Intravenous Corticosteroids Plus Placebo
Exclude patients who discontinue/withdraw
Exclude patients who discontinue/withdraw
Assess at Day 3 and Day 7 (Number of Stools and CRP)
Assess at Day 3 and Day 7 (Number of Stools and CRP)
Response
No Response
Response
No Response
Continue till Day 7
Salvage therapy
Continue till Day 7
Salvage therapy
Corticosteroid Refractory
Corticosteroid Refractory
Analyze for Primary Endpoint
Continue oral orticosteroids in tapering dose plus tofacitinib 10 mg BD till week 8
Continue oral corticosteroids plus standard of care (5-ASA ± Azathiopurine) in tapering dose till week 8
Analyze for Secondary Endpoints

Figure 5: Design of the study

SOURCES OF DATA

Patients diagnosed with acute severe ulcerative colitis as per modified Truelove and Witt's criteria admitted indoors in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, Punjab, India were enrolled for the study.

METHODS OF COLLECTION OF DATA

Confirmed cases of IBD were enrolled and the appropriate investigations were done. Daily stool frequency and questionnaire were filled. Patients were followed-up every day for first 7 days followed by on day 14 and after 8 weeks from the day of enrollment into the study.

SCALES AND SCORES

Acute Severe Ulcerative Colitis will be defined on the basis of modified Truelove and Witts Criteria.

Parameter	Mild	Moderate	Severe
Bloody stool/day	<4	≥4 or more if	≥6 and
Pulse	<90 bpm	≤90 bpm	> 90 bpm or
Temperature	<37.5 C	≤ 37.8 C	> 37.8 C or
Haemoglobin	>11.5 g/dL	>10.5 g/dL	<10.5 g/dL
ESR or	<20 mm/h	≤ 30 mm/h	>30 mm/h or
CRP	normal	≤ 30 mg/l	>30 mg/l

Table 6: Modified Truelove and Witts Criteria [31]

Disease Classification

- The Montreal Classification will be used to classify the disease extent of UC.

Montreal Classification for adult UC		
Term	Distribution	Description
E1	Proctitis	Involvement limited to the rectum (i.e. proximal extent of inflammation is distal to the recto-sigmoid junction)
E2	Left sided colitis	Left-sided involvement limited to the proportion of the colon distal to the splenic flexure (analogous to 'distal' colitis)
E3	Extensive colitis	Extensive involvement extends proximal to the splenic flexure, including pancolitis

Table 7: Montreal classification of Ulcerative Colitis (UC) [35]

Disease severity

- Disease severity will be defined by the Mayo score.

Parameter	Score	Description
Stool frequency	0	Normal no. of stools for this patient
	1	1 to 2 stools more than normal
	2	3 to 4 stools more than normal
	3	5 or more stools more than normal
Rectal bleeding	0	No blood seen
	1	Streak of blood with stool less than half the time
	2	Obvious blood with stool most of the time
	3	Passing blood alone
Findings on endoscopy	0	Normal or inactive disease
	1	Mild disease (erythema, decreased vascular pattern, mild friability)
	2	Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
	3	Severe disease (spontaneous bleeding, ulcerations)
Physician's global assessment	0	Normal
	1	Mild disease
	2	Moderate disease
	3	Severe disease

Table 8: Mayo Clinic Score [99]

Definition of response to corticosteroids ± tofacitinib (Primary end point)

- Response: Defined as ≤3 stools/day with the absence of visible blood at day 7.
- Refractory: Patients with >8 stools/day, or 3–8 stools/day with CRP >45 mg/L at day 7.

Definitions of Secondary end points based on Mayo Clinic Score

- Clinical remission will be defined by a total Mayo score of 2 points or lower, with no individual sub-score exceeding 1 point and a rectal bleeding sub-score of 0.
- Clinical response will be defined by a decrease from baseline in Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the rectal bleeding sub-score of at least 1 point or absolute rectal bleeding sub-score of 0 or 1.

Duration of study

- The study duration was for one year (1st October 2021- 31st December 2022) with enrolment period of one year (1st October 2021- 30th September 2022) and a follow up period of 8 weeks for each enrolled subject.

OUTCOME

Endpoints

Primary Endpoint

To compare the rates of corticosteroid responsiveness in the two groups at Day3 and Day 7.

Secondary endpoints

To compare the proportion of patients in clinical remission at week 8.

Statistical analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Kolmogorov-Smirnov test. The cases in which the data was not normal, we used non-parametric tests. The following statistical tests were applied for the results:

1. The comparison of the variables which were quantitative and not normally distributed in nature were analysed using Mann-Whitney Test.
2. The comparison of the variables which were qualitative in nature were analysed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0.

For statistical significance, p value of less than 0.05 was considered statistically significant.

DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

- Yes, the study required investigations

The following investigations were carried out in all the enrolled subjects.

1. Hemogram.
    i. Hemoglobin.
    ii. TLC
    iii. Platelet count.
2. Erythrocyte Sedimentation Rate
3. C-Reactive Protein (quantitative)
4. Fecal Calprotectin (Quanton Cal Kit)
5. Liver Function Tests.
    i. AST (Aspartate aminotransferase).
    ii. ALT (Alanine aminotransferase).
    iii. ALP (Alkaline phosphatase).
    iv. Bilirubin.
    v. Total protein.
    vi. Albumin.
6. Renal Function Tests
    i. Blood Urea.
    ii. Serum Creatinine.
    iii. Serum electrolytes (sodium, potassium, chloride)
7. Fasting Blood Sugar.
8. Lipid profile
    i. Cholesterol (Total, HDL, LDL, VLDL)
    ii. Triglycerides
9. Hepatitis B surface antigen (HBs Ag)
10. Anti-Hepatitis C antibodies (Anti HCV)
11. Sigmoidoscopy (unprepared)
12. Stool for Clostridioides difficile toxin

13. Rectal biopsy for CMV and EBV (histopathology and immunohistochemistry)

Monitoring for Adverse Effects (AE)

Safety was assessed by physical examinations, clinical and laboratory results and the spontaneous reporting of AEs, in all subjects. AEs experienced by participants involved in the study were reported to the site's IEC in accordance with their procedures. Subjects were monitored for development of any infection (viral, bacterial, and fungal). A subject who experienced a serious infection (defined as any infection requiring parenteral antibiotics or hospitalization) was discontinued from the study. A serious infection would be reported as a serious adverse event (SAE). Subjects who experienced non-serious infections that required treatment were continued on the drug but a record was mentioned in the CRF. All enrolled subjects were followed closely for identification of a cardiovascular/ venous thromboembolism event.

HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION?

Attached herewith.

OBSERVATIONS & RESULTS

The present study “A prospective placebo controlled randomized clinical study of tofacitinib as an adjunct to corticosteroids in acute severe ulcerative colitis” was conducted at Dayanand Medical College and Hospital, Ludhiana. A total of 104 patients were enrolled and randomized to receive either tofacitinib plus corticosteroids (n=53) or corticosteroids alone (n=51). Primary outcomes were assessed at days 3 and 7. Subsequently the patients were followed till 8 weeks for use of medical or surgical rescue therapy.

Out of total 53 patients of Group 1, 29 (54.72%) were male whereas 24 (45.28%) were females. Similarly, the Group 2 had 30 (58.82%) males whereas 21(41.18%) were females. The difference in the gender wise distribution between the two groups is statistically insignificant (p=0.673).

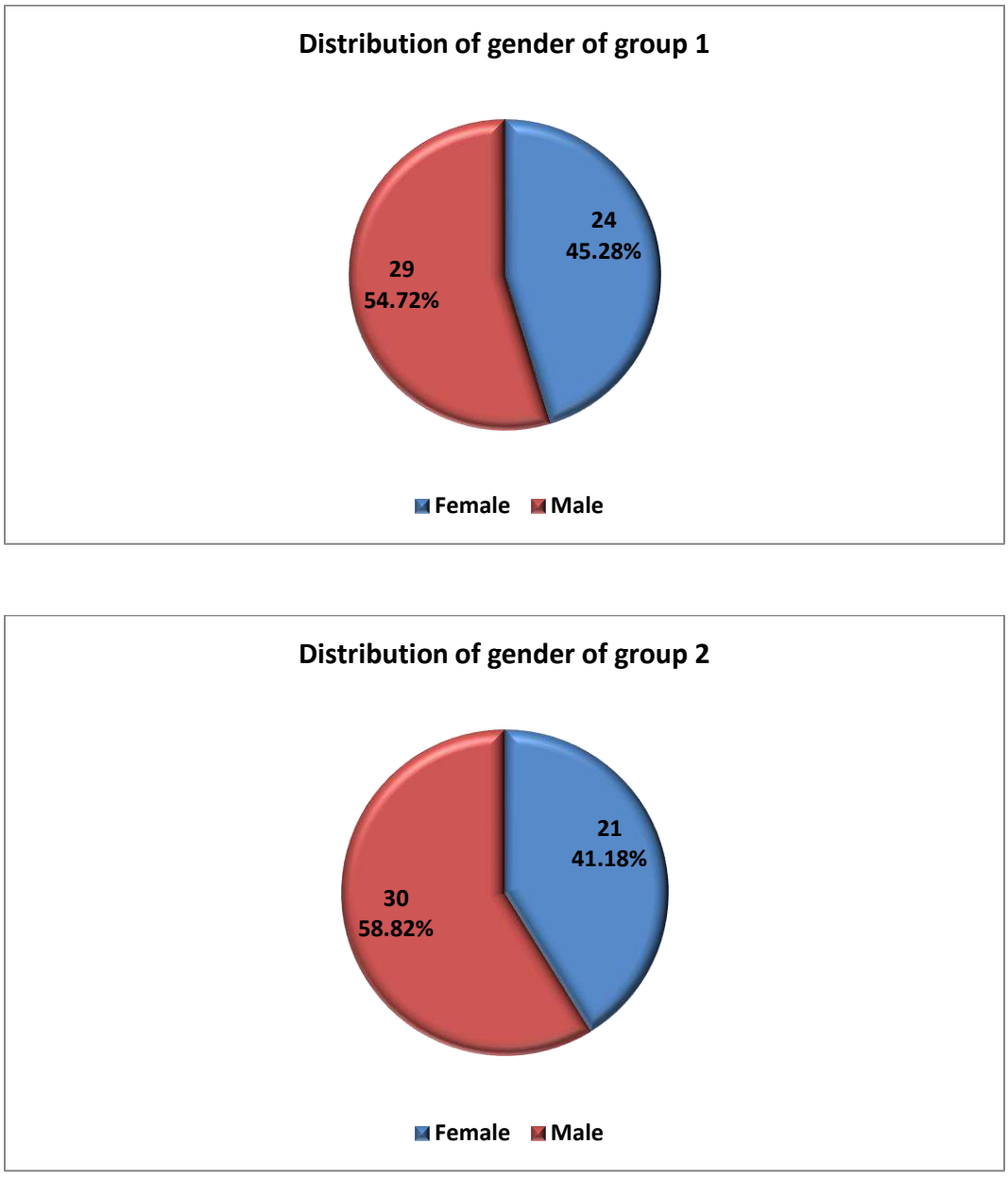

Figure 6: Gender wise distribution of Group 1 and Group 2

The mean age of study population of study population was 39.48 ± 14.8 (range 18-79 years). The mean age of patients in group 1 was 38.47±15.01 (range 18-79) years and in group 2 was a 40.53±14.65 (range 18-74) year .The difference in mean age of the two groups was statistically insignificant. (p= 0.232).

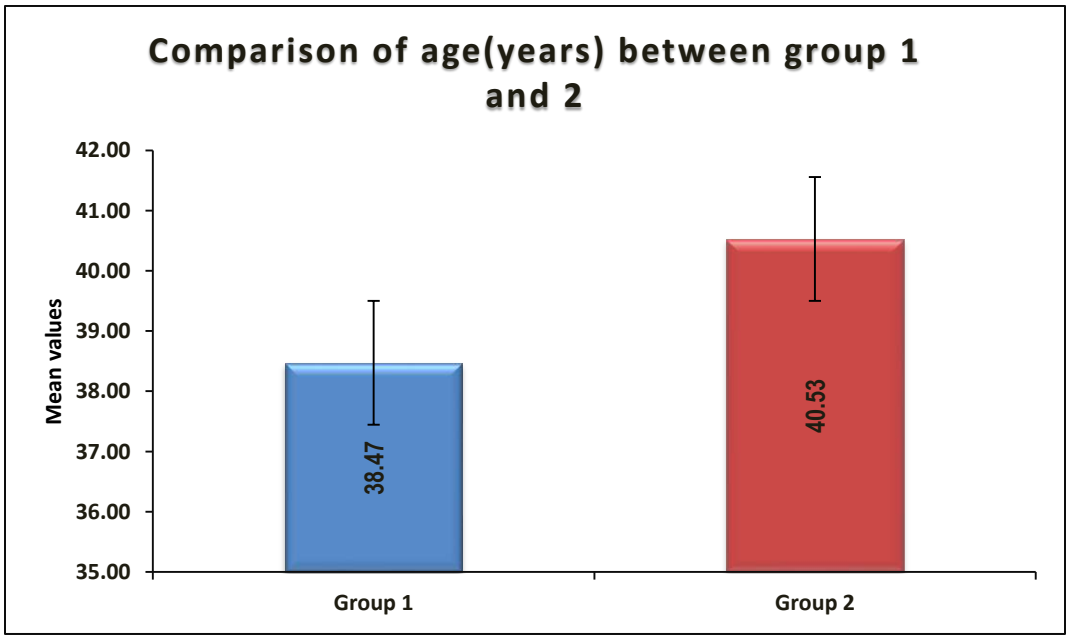

Figure 7: Comparison of age (years) between group 1 and 2

Thirty two patients in group 1 were in the age group of 18 - 40 years, 14 patients in 41 - 60 years and seven patients were aged >60 years whereas Group 2 had 27,18 and 6 patients in age categories 18-40 years, 41-60 years and >60 years respectively.

Baseline characteristics	Group 1(n=53)	Group 2(n=51)	Total	P value
Age(years)				
18-40	32 (60.38%)	27 (52.94%)	59 (56.73%)	0.618
41-60	14 (26.42%)	18 (35.29%)	32 (30.77%)	
>60	7 (13.21%)	6 (11.76%)	13 (12.50%)	
Mean ± SD	38.47 ± 15.01	40.53 ± 14.65	39.48 ± 14.8	0.481
Range	18-79	18-74	18-79	

Table 9: Study population: Age wise distribution.

The mean body mass index of patients in both the groups was similar (21.48±4.58 versus 21.68±4.03 kg/m^2 in Groups 1& 2, respectively) (p=0.973)

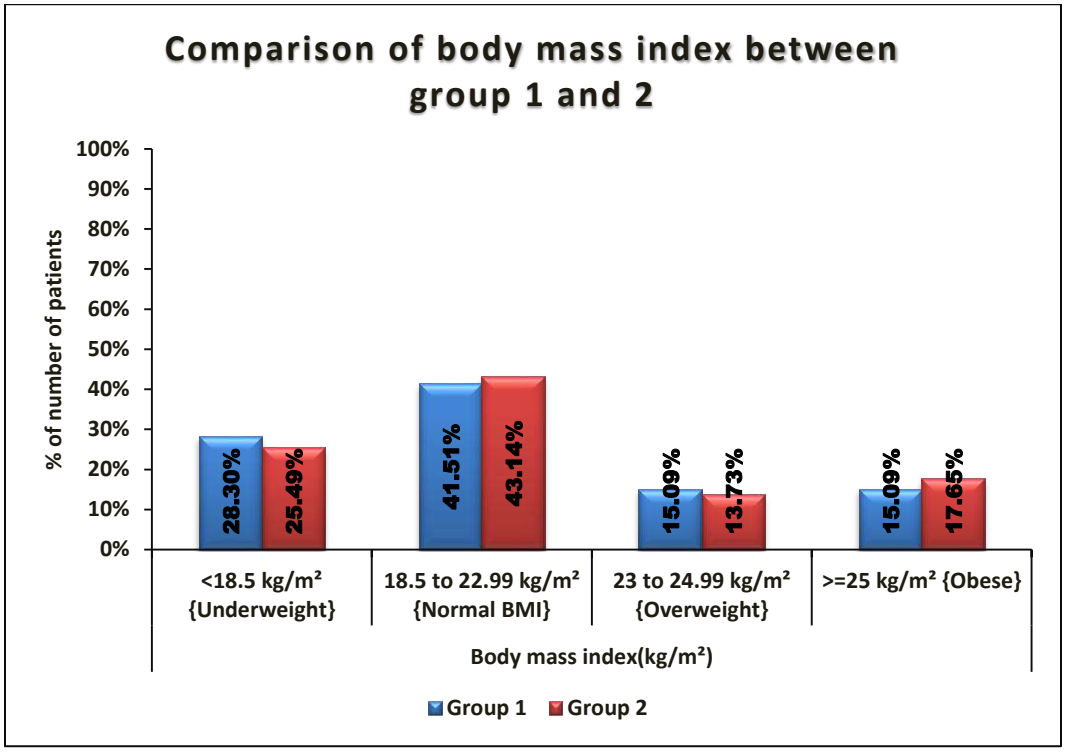

Figure 8: Comparison of body mass index (kg/m²) between group 1 and 2.

10 patients in group 1 had co morbid illnesses with diabetes mellitus being the most common, whereas three patients were hypertensive. Similarly, group 2 had 5 patients with co-morbid illnesses with hypertension being the most common (n=3).

Co-morbidities	Group 1(n=53)	Group 2(n=51)	Total
Diabetes	6 (11.32%)	1 (1.96%)	7 (6.73%)
Hypertension	3 (5.66%)	3 (5.88%)	6 (5.77%)
Hypothyroidism	1 (1.89%)	1 (1.96%)	2 (1.92%)

Table 10: Comparison of co-morbidities between group 1 and 2.

Thirty nine (73.58%) patients in Group 1 and 25(49.02%) patients in Group 2 had previous exposure to steroids. The difference was statistically significant between the two groups (p=0.01). The previous exposure to azathioprine (AZA) in the two groups was similar {8 (15.09%) versus 6 (11.76%) in Group 1 and Group 2, respectively} (p=0.619). The difference in exposure to anti-TNFs in both the groups {3 (5.66%) and 2 (3.92%) in Group 1 & Group2, respectively} was statistically insignificant (p=1).

Previous treatment given	Group 1 (n=53)	Group 2 (n=51)	Total	P value
Previous use of steroids	39 (73.58%)	25 (49.02%)	64 (61.54%)	0.01
Previous AZA	8 (15.09%)	6 (11.76%)	14 (13.46%)	0.619
Previous anti-TNFs	3 (5.66%)	2 (3.92%)	5 (4.81%)	1

Table 11: Comparison of previous treatment given between group 1 and 2.

The median duration of the disease was 3 and 2 years in Group 1 and 2, respectively.

Parameters	Group 1 (n=53)	Group 2 (n=51)	Total	P value
Duration of disease(years)				
Median(IQR)*	3(2-5)	2(1-4)	2(2-4.25)	0.009
Range	1-21	1-21	1-21	

Table 12: Comparison of duration of disease (years) between group 1 and 2 *IQR-Interquartile Range

The mean stool frequency in Group 1 was 10.32±3.63 per day whereas it was 10.18±3.3 in Group 2 respectively. The difference in stool frequency at day 0 between the two Groups was statistically insignificant (p=0.833)

Total stool frequency at day 0	Group 1 (n=53)	Group 2 (n=51)	Total	P value
Mean ± SD	10.32 ± 3.63	10.18 ± 3.3	10.25 ± 3.45	0.833

Table 13: Comparison of total stool frequency at day 0 between group 1 and 2.

Thirteen patients in group 1 had one systemic criteria of toxicity as per modified Truelove and Witts criteria, whereas 27 had two and 13 had three or more criteria. Similarly, 21, 24 and 6 patients in group 2 had one, two and three or more criteria of systemic toxicity, respectively.

Number of criteria of systemic toxicity in the Truelove and Witts Criteria	Group 1 (n=53)	Group 2 (n=51)	Total	P value
1	13 (24.53%)	21 (41.18%)	34 (32.69%)	0.353†
2	27 (50.94%)	24 (47.06%)	51 (49.04%)	
3	13 (24.53%)	6 (11.76%)	19 (18.27%)	
Total	53 (100%)	51 (100%)	104 (100%)	

Table 14: Comparison of number of criteria of systemic toxicity in the Truelove and Witts Criteria between group 1 and 2.

Unprepared sigmoidoscopy was done within 24 hours of hospitalization. The mean endoscopic Mayo score was 2.32 ± 0.47 in Group 1 versus 2.69 ± 0.47 in Group 2.

Parameter	Group 1 (n=53)	Group 2 (n=51)	Total
Endoscopic Mayo score			
Mean ± SD	2.32 ± 0.47	2.69 ± 0.47	2.5 ± 0.5
Range	2-3	2-3	2-3

Table 15: Comparison of Mayo Score between group 1 and 2.

The mean hemoglobin, platelet count, fasting blood sugar, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total cholesterol, low density lipoprotein (LDL), high density of lipoprotein (HDL), triglycerides, bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin and creatinine levels were similar in both the groups. However, significantly higher levels of fecal calprotectin levels were observed in Group 1 as compared to Group 2 (1982.32±128.71 in Group 1 versus 1750.57 ± 562.62 in Group 2)(p=0.006).

Laboratory parameters	Group 1 (n=53)	Group 2 (n=51)	Total cohort	P value
Hemoglobin (g/dL)	9.43 ± 2.37	10.3 ± 2.19	9.85 ± 2.31	0.055
Platelet count (cells/mm²)	371.64 ± 154.26	314.86 ± 147.72	343.8 ± 153.04	0.058
Fasting blood sugar (mg/dL)	106.79 ± 22.88	103.33 ± 12.69	105.1 ± 18.59	0.345
ESR (mm/hour)*	36(26-58)	34(19-63.5)	35(22-58.5)	0.956
CRP (mg/dL)*	47.37(14.25-75.48)	33.29(12.34-93.02)	44.12(13.515-79.135)	0.637
Fecal calprotectin(µg/gram)	1982.32 ± 128.71	1750.57 ± 562.62	1868.67 ± 419.02	0.006
Total cholesterol (mg/dL)	117.89 ± 34.32	119.71 ± 34.28	118.57 ± 34.08	0.825
LD L(mg/dL)	70.34 ± 26.25	69.25 ± 24.8	69.93 ± 25.55	0.86
HDL (mg/dL)	36.04 ± 14.12	38.5 ± 11.85	36.96 ± 13.29	0.442
Triglyceride (mg/dL)	107.51 ± 56.32	107.11 ± 63.22	107.36 ± 58.56	0.977
Total bilirubin (mg/dL)	0.47 ± 0.28	0.43 ± 0.23	0.46 ± 0.26	0.496
ALT (U/L)*	16(10-25)	16(9-23)	16(10-23.25)	0.806
AST (U/L)*	22(15-30)	17(14-21)	19(15-24)	0.127
ALP (U/L)*	83(73-120)	85(69.5-121)	83.5(71.75-120.25)	0.553
Albumin (g/dL)	3.05 ± 0.81	3.06 ± 0.91	3.05 ± 0.86	0.9680
Creatinine (mg/dL)	0.74 ± 0.27	0.75 ± 0.38	0.74 ± 0.32	0.862
Neutrophil lymphocyte ratio*	3.89(2.648-5.472)	4.39(2.51-8.891)	4.25(2.538-6.486)	0.288
CRP-albumin ratio*	17.72(5.766-32.934)	11.5(4.144-37.76)	14.89(4.719-35.163)	0.675

Table 16: Comparison of laboratory parameters between group 1 and 2. All values are expressed as mean±SD whereas *marked values are expressed as median (inter-quartile range)

Stool for *clostridoides difficile* (C.diff) infection (toxin A/B) was positive in 5(9.43%) patients in Group 1 and 6 (11.76%) patients in Group 2. The enteric biopsy obtained through unprepared sigmoidoscopy was analyzed for cytomegalovirus (CMV) infection on histology and Immunohistochemistry (IHC) along with screening for Epstein Barr virus (EBV) infections. CMV inclusion bodies were found positive in 3(5.66%) patients in group 1 and none in group 2. Ten (18.87%) patients in Group 1 and three patients in group 2 had IHC positivity for CMV. The differences between the two groups were statistically insignificant (p=0.243 and 0.073 for histopathology and IHC respectively). The EBER-ISH was positive in 3(5.66%) patients in Group 1 versus 5(9.80%) patients in Group 2 respectively (p= 0.484)

Variables	Group 1 (n=53)	Group 2 (n=51)	Total	P value
C diff	5 (9.43%)	6 (11.76%)	11 (10.58%)	0.699
CMV-H&E	3 (5.66%)	0 (0%)	3 (2.88%)	0.243
CMV-IHC	10 (18.87%)	3 (5.88%)	13 (12.50%)	0.073
EBV	3 (5.66%)	5 (9.80%)	8 (7.69%)	0.484

Table 17: Comparison of variables between group 1 and 2.

Outcome assessment

The treatment response was assessed as per the Travis criteria. The response was defined as < 3 stools per day or 3-8stools per day with C-reactive protein (CRP) <45mg/L whereas non-response was defined as ≥8 stools/day, or 3–8 stools/day with CRP ≥45 mg/L. A total of 42(79.25%) out of 53 patients of group 1 responded to treatment whereas 30 (58.82%) out of 51 patients responded in group 2 at day 3. The between-group difference in proportion of patients responding to treatment was statistically significant. (p=0.024)

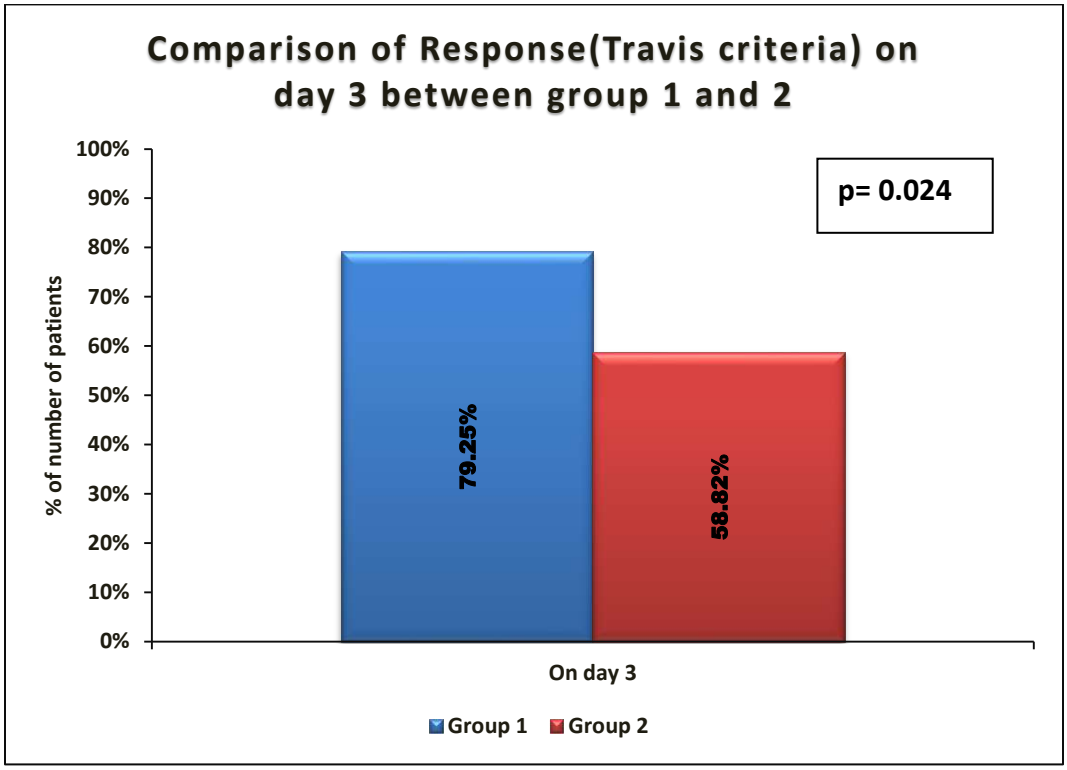

Figure 9: Comparison of Response (Oxford criteria) on day 3 between group 1 and 2.

The response to treatment on day 7 of the treatment was assessed as per Travis criteria. As per Travis criteria, 44(83.02%) out of 53 patients of group 1 responded to treatment whereas 31 (60.78%) out of 51 patients responded in group 2, on day 7.

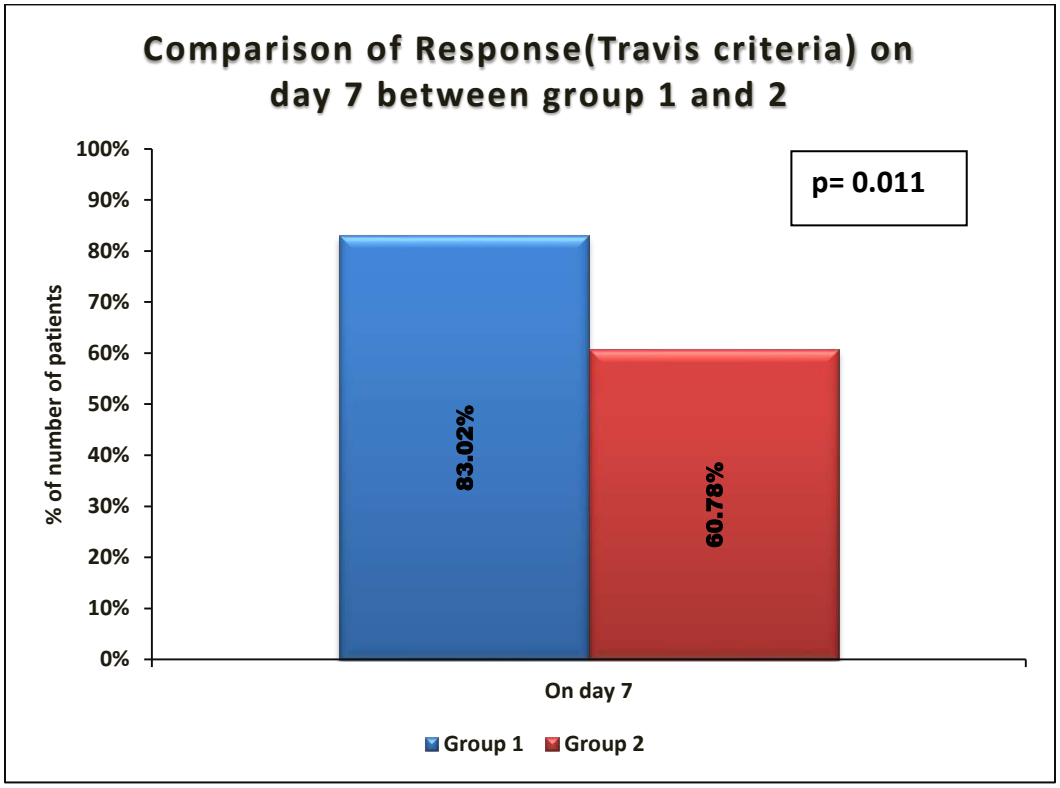

Figure 10: Comparison of Response (Oxford criteria) on day 7 between group 1 and 2.

Six (11.32%) patients in Group 1 received rescue treatment whereas 16(31.37%) patients in group 2 received rescue treatment by day 7. The difference in the use of rescue treatment between the two groups was statistically significant (p=0.012)

Outcome within 1 week	Group 1(n=53)	Group 2(n=51)	Total	P value
Need for rescue treatment	6 (11.32%)	16 (31.37%)	22 (21.15%)	0.012
Infliximab	5 (9.43%)	11 (21.57%)	16 (15.38%)	0.086
Colectomy	1 (1.89%)	5 (9.80%)	6 (5.77%)	0.109

Table 18: Comparison of outcome within 1 week between group 1 and 2.

The clinical remission at week 8 was defined as total Mayo score of 2 points or lower, with no individual sub-score exceeding 1 point and rectal bleeding sub-score of 0. 35(66.04%) patients in Group 1 and 23 (45.10%) in Group 2 were in clinical remission. The difference in proportion of patients in clinical remission between two groups was statistically significant (p=0.032). One patient (1.89%) in group 1 and 4(7.84%) patients in group 2 died during the study period. The difference in mortality rate between the two groups was statistically insignificant (p=0.201).Three patients were lost to follow-up in Group 1 whereas 2 patients of Group 2 were lost to follow-up. All these patients were considered as treatment failures. The colectomy free survival was 88.68% in Group 1 versus 72.55% in Group 2 respectively (p=0.037)

Outcome at week 8	Group 1	Group 2	Total	P value
Clinical remission	35 (66.04%)	23 (45.10%)	58 (55.77%)	0.032
Mortality	1 (1.89%)	4 (7.84%)	5 (4.81%)	0.201
Colectomy free survival	47 (88.68%)	37 (72.55%)	84 (80.77%)	0.037

Table 19:-Comparison of outcome at 8th to 12th week between group 1 and 2.

A total of 17 patients in Group 1 and 15 patients in group 2 had adverse effects during the study period with facial edema being the most common {4 (7.55%) patients in group 1 and 13(25.49%) patients in group 2}. The other adverse effects are summarized in Table.

Adverse effect	**Group 1 (n=53)**	**Group 2 (n=51)**	**Total**
Facial edema	4 (7.55%)	13 (25.49%)	17 (16.35%)
Dural venous sinus thrombosis	1 (1.89%)	0 (0%)	1 (0.96%)
Arthralgia	1 (1.89%)	0 (0%)	1 (0.96%)
Hair loss	5 (9.43%)	1 (1.96%)	6 (5.77%)
Acne	3 (5.66%)	0 (0%)	3 (2.88%)
Pruritus	1 (1.89%)	0 (0%)	1 (0.96%)
URTI	1 (1.89%)	0 (0%)	1 (0.96%)

Table 20: Comparison of adverse effect between group 1 and 2.

DISCUSSION

This is the first study to evaluate the use of tofacitinib upfront in the management of ASUC along with corticosteroids. Tofacitinib as an add on treatment improved treatment responsiveness in patients with ASUC at day 3 and day 7 of the treatment. There was significantly higher proportion of patients responsive to treatment in tofacitinib arm as compared to placebo arm (79.25% versus 58.82%; p=0.024) on day 3 and as well as on day 7 of the treatment (83.02% versus 60.78%; p=0.011)

Moreover, fewer patients required rescue medical or surgical treatment within seven days of hospitalization (6 in tofacitinib plus corticosteroid group versus 16 in corticosteroid alone). The difference was statistically significant (p=0.012). The infliximab was required in 5 patients in tofacitinib arm whereas in 11 patients in placebo arm. Similarly, higher number of patients required colectomy in the corticosteroid alone group in comparison with tofacitinib plus corticosteroid group.

The benefit with the addition of tofacitinib along with intra-venous corticosteroids is not only limited to initial 7 days and extend beyond it with cumulative probability of need for rescue treatment at 8 weeks was also significantly lower in the combination arm as compared to placebo arm. Therefore, the addition of tofacitinib has beneficial effect both on short and long-term outcome of ASUC. The plausible explanation for the same can be pan-JAK effect of tofacitinib hindering with the actions of interleukins and other inflammatory mediators

The addition of tofacitinib also had a positive bearings on the mortality associated with ASUC. Only one patient died in tofacitinib plus corticosteroids group by week 8 of the treatment whereas four patients died in the corticosteroid alone group. Moreover, the colectomy free survival was also higher in the tofacitinib arm as compared to placebo arm. Additionally, due to favorable pharmacokinetics, including quick onset of action clearance and rapid clearance, tofacitinib may be worthwhile in patients being contemplated for colectomy

The choice of optimal maintenance therapy in ASUC patients who respond to corticosteroids is unclear. Although, azathioprine (AZA) is the most commonly used in this clinical setting but the long term disease course is poorly defined. In a multicenter retrospective study, the probabilities of relapse free survival and colectomy-free survival were 58%, 48% and 40% and 96%,95% and 91% at 1,2 and 5 years respectively. Multivariate analysis revealed that maintenance with biologics has lower rates of relapse. [100] The use of biologics in developing countries like India is limited, which struggle to find a striking balance between the healthcare costs and potential adverse effects like malignancy, infections, etc. associated with medications. The continuation of treatment with tofacitinib beyond seven days, in reduced doses, also yielded excellent results and provides an effective therapeutic option for maintenance of remission in these patients, though the long term outcomes are yet to be evaluated. In the current study, maintenance therapy with tofacitinib was associated with lower rates of use of medical or surgical rescue therapy until week 8 compared to maintenance therapy with azathioprine. One of the plausible explanations for this outcome can be the continuation of use of same drug used as induction therapy. AZA has slow onset of action and require at least 12-16 weeks before achieving therapeutic efficacy.

The most common treatment related adverse effect observed in the current study was facial edema. It was observed in 4 patients in tofacitinib arm as compared to 13 in the placebo arm. Hair loss, acneiform skin eruptions, upper respiratory tract infections, etc. were the other common encountered adverse effects during the study period. Although, tofacitinib has been reported to be associated with increased risk of major adverse cardiovascular events (MACE) in patients with rheumatoid arthritis but the same findings have not been replicated in patients with UC. The risk of thromboembolic events with tofacitinib in UC has been comparable to anti-

TNF agents. [101] Recently, the post hoc analysis of the data from UC clinical program demonstrated increased incidence of adverse events including MACE, with increasing age (>65years). [102] However, the number of patients in the age group of> 65 years was small. A recent systematic review, including 148 patients, reported the safety of tofacitinib in ASUC, with venous thromboembolism and death reported in only one patient each. [98] Our study also had only one incidence of hemorrhagic infarct and dural venous sinus thrombosis in the tofacitinib arm. This thrombotic event could be attributed to tofacitinib. However, ASUC has itself being a pro-thrombotic state secondary to inflammation and concomitant use of corticosteroids might also have contributed to the development of venous sinus thrombosis.

A total of five (4.84%) patients died during the study period. The mortality in the current study was higher than previously reported mortality rates. This could be attributed to a severe disease phenotype at presentation. Approximately 50% of the patients were on oral corticosteroids at the time of hospitalization. Also, majority of the patients (67.31%) had 2 or more criteria of systemic toxicity in the Truelove and Witts criteria and nearly two-thirds (67.31%) had deep ulcers on the index sigmoidoscopy.

Despite an increased immune suppression in the combination treatment arm, the risk of infectious complications or adverse effects was comparable to the placebo arm.

This is the first ever study employing tofacitinib as first line treatment in ASUC, albeit in combination with corticosteroid. Moreover, this study had a placebo arm to compare the outcomes, which further increase the power and reliability of study.

The study also had few limitations. It is a single center study and the effect of geographical and ethnic factors on the outcomes couldn’t be assessed; although, this study was adequately powered to demonstrate the efficacy of tofacitinib in improving treatment response in patients with ASUC. The optimal dose of tofacitinib couldn’t be ascertained from the study and

larger RCTs are required to ascertain the same. There was no formal cost analysis done in the study.

Thus, it can be safely concluded from the current study that tofacitinib as an add-on therapy to corticosteroids improved treatment responsiveness and decreased the need for medical or surgical rescue therapy at 8 weeks. Future studies assessing tofacitinib monotherapy as first line therapy versus corticosteroids, dosing strategies, and long term outcomes are needed before tofacitinib is positioned in the therapeutic algorithms of ASUC.

SUMMARY AND CONCLUSION

Ulcerative Colitis (UC) is a chronic relapsing and remitting immune-mediated inflammatory condition of the large intestine that is associated with inflammation of the rectum but often extends proximally to involve additional areas of the colon. The complex interplay of genetic predisposition, environmental factors, epithelial barrier defects, dysregulated immune responses, microbiological factors and environmental factors are hypothesized to play a key role in disease pathogenesis.

This was a prospective placebo controlled randomized clinical study to study the efficacy of tofacitinib as an adjunct to corticosteroids in acute severe ulcerative colitis. The ASUC was diagnosed as per modified Truelove and Witts criteria. A total of 104 patients satisfying inclusion and exclusion criteria were enrolled into the study after obtaining informed consent. All these patients were randomized into two groups. Group 1 patients (n=53) received tofacitinib as an adjunct to corticosteroids in the management of ASUC. Group 2 patients (n=51) received similar looking placebo as an adjunct to corticosteroids. Index sigmoidoscopy was done at the time of admission. The subjects were followed up till week 8 of the treatment.

The baseline demographic and disease activity characteristics were comparable between the two groups. The baseline laboratory parameters such as hemoglobin, C-reactive protein, erythrocyte sedimentation rate, etc. were also similar between the two groups.

The responsiveness to treatment was assessed as per Travis criteria defined as total number of stools <3 per day or total stool frequency of 3-8 per day along with C-reactive protein less than 45mg/L. The treatment responsiveness was assessed on day 3 and day 7 of the treatment. On day 3 of the treatment, 42 (79.25%) out of 53 patients of group 1 had response to the treatment whereas 30 (58.82%) out of 51 patient responded in group 2. The difference in proportion between the two

groups was statistically significant. (p=0.024) Similarly, 44(83.02%) patients of group 1 responded to the treatment as per Travis criteria and 31 (60.78%) patients of group 2 responded. The difference in proportion of patients responsiveness to day 7 of the treatment was significantly higher in group 1 in comparison to group 2 (p=0.011)

The need for rescue therapy was significantly lower in group 1 in comparison to group 2 (p=0.012). Sixteen patients in group 2 required rescue therapy whereas 6 patients require in group 1. 5 patients required infliximab as rescue therapy whereas 1 patient underwent colectomy. Similarly, 11 and 5 patients required infliximab and colectomy, respectively.

The clinical remission at week 8 was defined as total Mayo score of 2 points or lower, with no individual sub-score exceeding 1 point and rectal bleeding sub-score of 0. A total of 35 (66.04%) patients in Group 1 and 23 (45.10%) in Group 2 were in clinical remission and the difference in proportion of patients in clinical remission between two groups was statistically significant (p=0.032). One patient (1.89%) in group 1 and 4(7.84%) patients in group 2 died during the study period. The difference in mortality rate between the two groups was statistically insignificant (p=0.201).Three patients were lost to follow-up in Group 1 whereas 2 patients of Group 2 were lost to follow-up. All these patients were considered as treatment failures. The colectomy free survival was significantly higher in group 1 (88.68% in group 1 versus 72.55% in group 2, respectively) (p=0.037)

This is the first ever study employing tofacitinib as first line treatment in ASUC, albeit in combination with corticosteroids. The study also had few limitations. It is a single center study and the effect of geographical and ethnic factors on the outcomes couldn’t be assessed. The optimal dose of tofacitinib couldn’t be ascertained from the study and larger RCTs are required to ascertain the same. There was no formal cost analysis done in the study.

Thus, it can be safely concluded from the current study that tofacitinib as an add-on therapy to corticosteroids improved treatment responsiveness and decreased the need for medical or surgical rescue therapy at 8 weeks.

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					Duration of Stay				Previous treatment			Day 0		treatment at discharge				
Group	Intials	Age	Sex	MRD	number of days in ward	number of days in ICU	TOTAL STAY IN HOSPITAL	Previous flares	Previous use of steroids	Previous AZA	Previous anti-TNFs	baseline HR	baseline temperature	5-ASA	Thiopurines	Steroids	Tofacitinib	IFX
1	BS	62	MALE	936632	5	0	5	6	YES	NO	NO	88	97.2	YES	NO	YES	YES	NO
1	MK	28	FEMALE	1188595	10	0	10	2	YES	NO	NO	96	98.2	YES	NO	YES	YES	NO
1	SS	22	MALE	1023626	7	0	7	0	YES	NO	NO	92	97.6	YES	NO	YES	YES	NO
1	NK	39	FEMALE	1267414	8	0	8	Multiple	YES	NO	NO	80	98	YES	NO	YES	YES	NO
1	VK	44	FEMALE	1277308	9	0	9	1	YES	YES	NO	88	99	YES	NO	YES	YES	NO
1	JK	18	FEMALE	1274147	10	4	14	2	NO	YES	NO	120	98	YES	NO	YES	YES	NO
1	D	43	MALE	695368	4	0	4	1	YES	NO	NO	122	99.4	YES	NO	YES	YES	NO
1	BS	60	MALE	528432	16	0	16	1	YES	NO	NO	99	97.9	YES	NO	YES	YES	NO
1	VK	28	MALE	1144993	9	0	9	0	YES	NO	NO	114	99.6	NO	NO	YES	YES	NO
1	NK	27	MALE	1141268	7	0	7	0	NO	NO	NO	108	102	YES	NO	YES	YES	NO
1	S	46	FEMALE	1128697	23	0	23	0	NO	NO	NO	96	98	NO	NO	YES	YES	NO
1	AK	23	MALE	1130712	8	0	8	0	YES	NO	NO	94	97.4	YES	NO	YES	YES	NO
1	GS	50	MALE	1133477	0	10	10	0	NO	NO	NO	98	97.8	YES	NO	YES	YES	NO
1	PK	38	FEMALE	77126	9	0	9	3	YES	YES	NO	120	98.2	YES	NO	YES	YES	NO
1	A	26	FEMALE	799442	6	0	6	1	NO	NO	NO	108	98.8	YES	NO	YES	YES	NO
1	SK	25	MALE	1167558/1158335	7	0	7	0	NO	NO	NO	112	98.4	YES	NO	YES	YES	NO
1	TK	65	MALE	1162070	7	0	7	0	YES	NO	NO	93	98.8	YES	NO	YES	YES	NO
1	PS	39	MALE	188642	7	0	7	0	YES	NO	NO	95	98.6	YES	NO	YES	YES	NO
1	NS	48	MALE	1203611	6	0	6	0	YES	NO	NO	110	98	YES	NO	YES	YES	NO
1	KK	32	FEMALE	1235301	9	0	9	3	YES	NO	NO	78	99.1	YES	NO	YES	YES	NO
1	H	26	MALE	1112850	6	0	6	0	YES	NO	NO	112	98.6	YES	NO	YES	YES	NO
1	RB	32	FEMALE	1183154	7	0	7	0	YES	NO	NO	92	98.4	YES	NO	YES	YES	NO
1	SK	44	FEMALE	1098251	6	0	6	0	YES	NO	NO	86	98.9	YES	NO	YES	YES	NO
1	K	26	MALE	1168251	7	0	7	0	YES	YES	NO	90	98.6	YES	NO	YES	YES	NO
1	GC	70	MALE	1137609	7	0	7	0	NO	NO	NO	103	99.4	YES	NO	YES	YES	NO
1	CK	37	FEMALE	1141123	14	0	14	0	YES	NO	NO	110	98.4	YES	NO	YES	YES	NO
1	MA	43	MALE	1187390	9	0	9	0	NO	NO	NO	131	98.6	YES	NO	YES	YES	NO
1	AS	30	MALE	1034454	13	0	13	0	YES	NO	NO	109	98.7	YES	NO	YES	YES	NO
1	RK	61	FEMALE	417076	8	0	8	Multiple	YES	YES	NO	86	98.3	YES	NO	YES	YES	NO
1	VG	24	MALE	1177090	14	0	14	0	YES	NO	NO	96	98.5	YES	NO	YES	YES	NO
1	LS	24	MALE	1337209	6	0	6	0	YES	NO	NO	90	98.5	YES	NO	YES	YES	NO
1	MK	24	FEMALE	1326693	4	0	4	0	YES	NO	NO	80	97	YES	NO	YES	YES	NO
1	VS	18	MALE	1353093	6	0	6	0	NO	NO	NO	70	96.2	YES	NO	YES	YES	NO
1	DL	40	FEMALE	802939	8	0	8	1	YES	NO	NO	82	98.2	YES	NO	YES	YES	NO
1	HK	79	MALE	1217119	9	0	9	0	NO	NO	NO	112	99.4	YES	NO	YES	YES	NO
1	DK	56	FEMALE	1164721/869599/805869	11	0	11	0	YES	NO	NO	112	98.5	YES	NO	YES	YES	NO
1	DK	26	FEMALE	1238899	7	0	7	0	YES	NO	NO	89	97.2	YES	NO	YES	YES	NO
1	M	43	FEMALE	1134144	9	0	9	0	YES	NO	NO	94	98.7	YES	NO	YES	YES	NO
1	AK	24	FEMALE	1186666/1299704	7	0	7	2	NO	NO	NO	98	97	YES	NO	YES	YES	NO
1	VT	47	MALE	1113115	8	0	8	0	NO	NO	NO	101	98	YES	NO	YES	YES	NO
1	PS	21	MALE	62020	6	0	6	2	YES	NO	NO	100.8	98	YES	NO	YES	YES	NO
1	JK	62	FEMALE	1358940	6	0	7	-	NO	NO	NO	88	98.4	YES	NO	YES	YES	NO
1	BK	44	FEMALE	217923	5	0	5	Multiple	YES	YES	YES	78	99.7	YES	NO	YES	YES	NO
1	SK	23	FEMALE	1197931	6	0	6	0	YES	NO	NO	96	98.4	YES	NO	YES	YES	NO
1	SS	35	MALE	1323355	5	0	5	-	NO	NO	NO	97	98.9	YES	NO	YES	YES	NO
1	SK	34	MALE	1337808	11	0	11	0	YES	YES	YES	120	98.6	YES	NO	YES	YES	NO
1	SK	57	FEMALE	1240118	7	0	7	0	YES	NO	NO	84	97.4	YES	NO	YES	YES	NO
1	GS	28	MALE	1395284	7	0	7	0	YES	NO	NO	64	98.4	NO	NO	YES	YES	NO
1	YS	29	MALE	198625	10	0	10	2	YES	YES	YES	88	98.8	YES	NO	YES	YES	NO
1	AS	37	MALE	1401455	0	10	10	1	YES	NO	NO	84	98.6	YES	NO	YES	YES	NO
1	R	23	MALE	1155939	9	0	9	1	YES	NO	NO	104	98.6	YES	NO	YES	YES	NO
1	RK	62	FEMALE	1171779	8	0	8	Multiple	YES	NO	NO	110	98.6	YES	NO	YES	YES	NO
1	S	47	FEMALE	1128697	23	0	23	0	YES	NO	NO	96	98	NO	NO	YES	YES	NO

		Addictions				comorbidities														
Year of Diagnosis	Disease Duration	Alcohol	Smoking	Opium	IVDU	Diabetes	Hypertension	Hypothyroidism	CAD	COAD	Others	Chicken Pox	Shingles	Weight	Height inches	Ht in m	BMI	Stool Freq. during Day	SCCAI Score Day	Stool freq. during night
2020	3	-	-	-	-	Y	-	-	-	-	-	-	-	50	68	1.7272	16.76041414	5	1	5
2019	4	-	-	-	-	-	-	-	-	-	-	-	-	56.6	62	1.5748	22.82262629	4	1	3
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	56.6	62	1.5748	22.82262629	8	3	6
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	59.8	64	1.6256	22.62943979	6	1	5
2018	5	-	-	-	-	-	-	-	-	-	-	Y	-	76	65	1.651	27.88171257	11	3	5
2019	4	-	-	-	-	-	-	-	-	-	-	Y	-	52	61	1.5494	21.66088718	6	1	2
2018	5	-	-	-	-	-	-	-	-	-	-	-	-	70	66	1.6764	24.90822245	6	1	4
2018	5	-	-	-	-	Y	-	-	-	-	-	-	-	80	66	1.6764	28.46653995	5	1	4
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	70	62	1.5748	28.2258629	6	1	3
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	65	67	1.7018	22.44379628	6	1	4
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	75	60	1.524	32.29173125	7	2	6
2020	3	-	-	-	-	-	-	-	-	-	-	-	-	45	67	1.7018	15.53801281	6	1	4
2020	3	-	-	-	-	-	-	-	-	-	-	-	-	60	71	1.8034	18.44875739	4	1	3
2014	9	-	-	-	-	-	-	-	-	-	-	-	-	59	65	1.651	21.6450137	8	2	4
2019	4	-	-	-	-	-	-	-	-	-	-	Y	-	49	64	1.6256	18.54251755	4	1	2
2019	4	-	-	-	-	-	-	-	-	-	-	-	-	70	69	1.7526	22.78937555	5	1	4
2017	6	Y	-	-	-	-	Y	-	-	-	-	-	-	62	70	1.778	19.61228412	6	1	6
2017	6	Y	-	-	-	-	-	-	-	-	-	-	-	55.8	70	1.778	17.65105571	6	1	3
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	72.7	70	1.778	22.99698477	6	1	3
2014	9	-	-	-	-	-	-	-	-	-	-	-	-	65.3	60	1.524	28.11533401	4	1	2
2020	3	-	-	-	-	-	-	-	-	-	-	-	-	52	70	1.778	16.44901249	7	2	5
2020	3	-	-	-	-	-	-	-	-	-	-	-	-	40	62	1.5748	16.12906452	5	1	2
2015	8	-	-	-	-	-	-	-	-	-	-	-	-	40	62	1.5748	16.12906452	8	2	4
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	50	60	1.524	21.52782083	7	2	4
2021	2	Y	-	-	-	Y	-	-	-	-	-	-	-	70	66	1.6764	24.90822245	10	3	6
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	66	64	1.6256	24.97563589	5	1	6
2021	2	-	-	-	-	-	Y	-	-	-	-	-	-	62.3	64	1.6256	23.5754866	6	1	3
2021	2	Y	Y	Y	-	-	-	-	-	-	-	-	-	66	66	1.6764	23.48489545	5	1	5
2002	21	-	-	-	-	Y	-	-	-	-	-	-	-	46	62	1.5748	18.54842419	8	2	1
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	53	64	1.6256	20.05619246	6	1	3
2021	2	-	-	-	-	-	-	-	-	-	-	Y	-	64.6	70	1.778	20.43473475	13	3	2
2020	3	-	-	-	-	-	-	-	-	-	-	-	-	51.8	62	1.5748	20.88713855	4	1	3
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	35.9	56	1.4224	17.74397681	5	1	2
2019	4	-	-	-	-	-	Y	Y	-	-	-	-	-	66	64	1.6256	24.97563589	15	3	10
2021	2	Y	-	-	-	Y	-	-	-	-	-	-	-	53.8	68	1.7272	18.03420562	3	0	4
2011	12	-	-	-	-	-	-	-	-	-	-	-	-	56	62	1.5748	22.58069032	8	2	1
2015	8	-	-	-	-	-	-	-	-	-	-	-	-	44.6	63	1.6002	17.41752035	7	2	2
2018	5	-	-	-	-	-	-	-	-	-	-	-	-	53.8	62	1.5748	21.69359177	3	0	3
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	38	65	1.651	13.94085628	6	1	3
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	40	66	1.6764	14.23326997	3	0	3
2014	9	-	-	-	-	-	-	-	-	-	-	-	-	60.5	66	1.6764	21.52782083	15	3	5
2021	2	-	-	-	-	Y	-	-	-	-	-	-	-	71	61	1.5494	29.57544211	5	1	4
2007	16	-	-	-	-	-	-	-	-	-	-	Y	-	47	60	1.524	20.23615158	7	2	3
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	31	62	1.5748	12.500025	8	2	3
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	76	68	1.7272	25.4758295	12	3	6
2022	1	Y	-	-	-	-	-	-	-	-	-	Y	-	56.9	67	1.7018	19.64695397	6	1	2
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	52.3	64	1.6256	19.79129935	6	1	3
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	55	68	1.7272	18.43645556	6	1	3
2014	9	-	-	-	-	-	-	-	-	-	-	-	-	75.7	70	1.778	23.94596626	7	2	0
2017	6	Y	Y	-	y	-	-	-	-	-	-	-	-	80	72	1.8288	23.91980093	6	1	4
2020	3	-	-	-	-	-	-	-	-	-	-	-	-	54	77	1.9558	14.11708001	5	1	4
2011	12	-	-	-	-	-	-	-	-	-	-	-	-	49	59	1.4986	21.81848661	9	2	2
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	75	59	1.4986	33.39564278	9	2	4

Day 0																			
SCCAI Score Night	Total stool	Stools with Blood	SCCAI Amount of blood	SCCAI Urgency of defecation	SCCAI General Well Being	SCCAI EIMs	Endo Mayo	SCCAI	Partial Mayo	Total Mayo	Abdominal Pain	Abdominal Tenderness	Need for anti diarrheal drugs	Stool Freq. during Day	SCCAI Day	Stool freq. during night	SCCAI Night	Total stool	CRP
2	10	10	1	2	3	0	2	9	8	10	1	0	1	1	0	1	1	2	5.8
1	7	6	2	2	4	0	2	10	9	11	2	1	0	3	0	1	1	4	21.98
2	14	14	3	3	4	0	3	15	9	12	2	1	0	8	2	6	2	14	17
2	11	7	2	2	4	0	3	11	9	12	2	1	0	6	1	2	1	8	23.71
2	16	16	2	3	3	0	2	13	9	11	1	0	0	5	1	3	1	8	40.57
1	8	6	2	2	3	0	2	9	9	11	1	0	0	2	0	0	0	2	6.5
2	10	6	3	2	4	0	2	12	9	11	2	1	0	5	1	2	1	7	9.45
2	9	9	3	3	4	0	2	13	9	11	2	1	0	3	0	3	1	6	17.72
1	9	6	2	1	3	0	3	8	9	12	1	0	0	2	0	2	1	4	10.49
2	10	6	3	2	4	0	2	12	9	11	2	1	0	4	1	2	1	6	42.23
2	13	8	3	3	4	0	2	14	9	11	3	1	0	5	1	2	1	7	81.99
2	10	7	2	3	4	0	3	12	9	12	3	1	0	2	0	0	0	2	5.4
1	7	6	3	2	3	0	3	10	9	12	1	0	0	2	0	0	0	2	26.24
2	12	10	3	3	4	0	3	14	9	12	3	1	0	3	0	2	1	5	0.83
1	6	6	2	1	4	0	2	9	9	11	1	0	0	3	0	1	1	4	35.55
2	9	6	2	2	3	0	3	10	8	11	1	0	0	3	0	2	1	5	6.26
2	12	7	3	2	4	0	2	12	9	11	3	1	0	2	0	0	0	2	5.8
1	9	6	3	1	3	0	2	9	9	11	1	0	0	2	0	0	0	2	3.9
1	9	6	3	1	3	0	2	9	9	11	1	0	0	6	1	1	1	7	5.23
1	6	6	3	1	3	0	2	9	9	11	1	0	0	4	1	4	2	8	19.24
2	12	6	3	2	4	0	2	13	9	11	3	1	0	4	1	3	1	7	12.85
1	7	6	2	2	4	0	3	10	9	12	3	1	0	4	1	4	2	8	43.21
2	12	6	2	1	4	0	2	11	9	11	1	0	0	3	0	2	1	5	3.32
2	11	6	2	1	4	0	2	11	9	11	1	0	0	5	1	3	1	8	198.14
2	16	9	3	3	4	0	2	15	9	11	1	0	0	7	2	4	2	11	10
2	11	7	3	2	4	0	2	12	9	11	1	0	0	2	0	1	1	3	20
1	9	6	2	3	3	0	2	10	9	11	0	0	0	6	1	1	1	7	144
2	10	7	3	2	4	0	2	12	9	11	1	0	0	5	1	3	1	8	17.88
1	9	6	2	2	4	0	2	11	9	11	1	0	0	3	0	1	1	4	25.57
1	9	6	2	3	4	0	3	11	8	11	1	0	0	5	1	2	1	7	97
1	15	8	2	2	3	0	2	11	9	11	0	0	0	6	1	2	1	8	24.33
1	7	6	2	2	3	0	2	9	9	11	1	0	0	3	0	1	1	4	2.18
1	7	7	2	2	3	0	2	9	9	11	1	0	0	2	0	0	0	2	10.8
2	25	15	2	3	4	0	2	14	9	11	1	0	0	4	1	4	2	8	22.22
2	7	6	2	3	2	0	2	9	8	10	2	0	0	2	0	0	0	2	12.2
1	9	6	2	2	4	0	2	11	9	11	1	0	0	1	0	1	1	2	1.03
1	9	6	2	1	3	0	2	9	9	11	1	0	0	1	0	1	1	2	6.57
1	6	6	2	3	3	0	2	9	9	11	1	0	0	2	0	0	0	2	2
1	9	6	2	1	3	0	3	8	9	12	1	0	0	3	0	1	1	4	24.62
1	6	6	2	3	3	0	3	9	9	12	1	0	0	4	1	3	1	7	8.21
2	20	9	1	2	3	0	2	11	9	11	1	0	1	7	2	2	1	9	49.8
2	9	6	2	2	4	0	3	11	9	12	2	1	0	3	0	3	1	6	29.57
1	10	10	2	2	4	0	2	11	9	11	2	1	0	3	0	1	1	4	2.79
1	11	7	2	2	4	0	2	11	9	11	2	1	0	5	1	2	1	7	15.75
2	18	6	2	2	4	0	3	13	9	12	2	1	1	3	0	2	1	5	25.4
1	8	6	3	1	2	0	2	8	8	10	1	0	0	3	0	1	1	4	38.21
1	9	6	2	1	3	0	2	8	9	11	1	0	0	2	0	2	1	4	8.6
1	9	9	3	2	3	0	3	10	9	12	2	1	0	3	0	2	1	5	84.91
0	7	7	3	3	2	0	3	10	7	10	1	0	0	5	1	0	0	5	8.32
2	10	7	2	3	3	0	3	11	9	12	2	1	0	4	1	4	2	8	114.65
2	9	6	2	3	3	0	2	11	8	10	2	1	0	2	0	1	1	3	43.04
1	11	6	2	2	2	0	2	9	7	9	1	0	0	5	1	2	1	7	122.3
2	13	8	2	3	3	0	3	12	8	11	1	0	0	5	1	2	1	7	60

Day 3																	
Response at Day 3 Oxford criteria	Stools with Blood	SCCAI Amount of blood	SCCAI Urgency of defecation	SCCAI General Well Being	SCCAI EIMs	SCCAI	Abdominal Pain	Abdominal Tenderness	Need for anti diarrheal drugs	Stool Freq. during Day	SCCAI Day	Stool freq. during night	SCCAI Night	Total stool	CRP	Response Day 5 OXFORD CRITERIA	Stools with Blood
Y	0	0	0	1	0	2	0	0	0	1	0	0	0	1	59.9	y	0
Y	3	1	1	3	0	6	1	0	0	2	0	1	1	3	12.03	y	1
N	14	2	3	4	0	13	0	0	1	6	1	4	2	10	7.27	-	6
Y	2	2	1	3	0	8	1	0	0	3	0	2	1	5	9.76	y	1
Y	9	2	2	3	0	9	1	0	0	2	0	0	0	2	30.8	y	2
Y	2	1	1	2	0	4	0	0	0	2	0	0	0	2	6.17	y	0
Y	2	2	1	3	0	8	1	0	0	3	0	2	1	5	5.34	y	1
Y	5	2	3	4	0	10	0	0	0	3	0	2	1	5	6.08	y	3
Y	0	0	1	2	0	4	0	0	0	2	0	2	1	4	2.08	y	0
Y	2	2	1	3	0	8	1	0	0	4	1	0	0	4	31.13	y	1
N	3	2	1	3	0	8	1	0	0	4	1	2	1	6	60.28	-	2
Y	2	2	1	2	0	5	0	0	0	2	0	0	0	2	11.52	y	1
Y	1	2	1	2	0	5	0	0	0	2	0	0	0	2	4.07	y	1
Y	1	1	0	3	0	5	1	0	0	2	0	1	1	3	0.15	y	0
Y	0	0	1	2	0	4	0	0	0	2	0	0	0	2	14.56	y	0
Y	2	2	2	3	0	8	1	0	0	3	0	2	1	5	1.23	y	2
Y	1	2	1	3	0	6	1	0	0	2	0	0	0	2	0.27	y	1
Y	2	2	1	2	0	5	0	0	0	2	0	0	0	2	4.55	y	0
Y	2	1	1	2	0	6	0	0	0	2	0	1	1	3	3.88	y	1
Y	5	2	1	3	0	9	1	0	0	6	1	3	1	9	17.97	-	1
Y	3	2	2	3	0	9	1	0	0	3	0	1	1	4	0.23	y	1
Y	4	2	2	4	0	11	0	0	0	4	1	3	1	7	14.37	y	5
Y	2	2	1	3	0	7	1	0	0	3	0	1	1	4	1.96	y	0
N	2	1	1	3	0	7	1	0	0	2	0	1	1	3	29.57	y	1
N	4	2	3	3	0	12	1	0	1	3	0	2	1	5	5.15	y	1
Y	1	2	1	3	0	7	1	0	0	2	0	0	0	2	8.48	y	1
N	3	1	2	2	0	7	0	0	0	3	0	0	0	3	89.23	-	0
Y	2	2	1	3	0	8	1	0	0	4	1	1	1	5	13.65	y	1
Y	1	1	1	2	0	5	0	0	0	1	0	1	1	2	8.66	y	1
N	3	2	3	4	0	11	0	0	0	4	1	2	1	6	98.23	-	1
Y	5	2	2	2	0	8	0	0	0	4	1	1	1	5	11.33	y	1
Y	1	1	1	2	0	5	0	0	0	2	0	1	1	3	1.98	y	1
Y	0	0	0	2	0	2	0	0	0	2	0	0	0	2	20.84	y	0
Y	4	2	3	4	0	12	0	0	0	3	0	1	1	4	11.8	y	1
Y	0	0	0	1	0	1	0	0	0	2	0	0	0	2	26.13	y	0
Y	1	1	1	1	0	4	0	0	0	5	1	1	1	6	0.44	y	2
Y	0	0	1	3	0	5	1	0	0	2	0	0	0	2	5	y	0
Y	0	0	1	2	0	3	0	0	0	3	0	1	1	4	1.9	y	0
Y	0	0	0	2	0	3	0	0	0	1	0	0	0	1	18.34	y	0
Y	3	2	2	2	0	8	0	0	0	3	0	2	1	5	6.04	y	2
N	8	1	1	3	0	8	1	0	0	3	0	2	1	5	18.58	y	1
Y	3	2	2	3	0	8	1	0	0	5	1	4	2	9	14.62	-	4
Y	1	1	1	3	0	6	1	0	0	2	0	0	0	2	0.79	y	0
Y	7	1	1	3	0	7	1	0	0	3	0	0	0	3	4.7	y	0
Y	2	1	1	2	0	5	0	0	0	2	0	0	0	2	28.88	y	0
Y	1	1	1	2	0	5	0	0	0	6	1	3	1	9	25.45	-	2
Y	0	0	1	2	0	4	0	0	0	4	1	1	1	5	124	-	4
N	3	2	2	2	0	7	0	0	0	3	0	1	1	4	21.18	y	2
Y	3	1	1	2	0	5	0	0	0	5	1	0	0	5	6.87	y	2
N	5	2	3	3	0	11	1	0	0	5	1	4	2	9	30.3	-	4
Y	1	1	2	2	1	7	0	0	0	2	0	0	0	2	6.54	y	0
N	2	1	2	2	0	7	0	0	0	4	1	1	1	5	4.56	y	0
N	3	2	2	2	0	8	0	0	0	5	1	1	1	6	65.7	-	2

Day 5								Day 7									
SCCAI Amount of blood	SCCAI Urgency of defecation	SCCAI General Well Being	SCCAI EIMs	SCCAI	Abdominal Pain	Abdominal Tenderness	Need for anti diarrheal drugs	Stool Freq. during Day	SCCAI Day	Stool freq. during night	SCCAI Night	Total stool	Stools with Blood	CRP	Response at Day 7 Oxford Criteria	Response at day 7	SCCAI Amount of blood
0	0	0	0	0	0	0	0	1	0	0	0	1	0	5.6	y	Y	0
1	0	2	0	4	0	0	0	2	0	0	0	2	0	5.12	y	Y	0
2	2	4	0	11	1	0	1	5	1	2	1	7	2	17	N	N	2
1	1	2	0	5	0	0	0	3	0	1	1	4	1	4.56	y	N	1
1	1	2	0	4	0	0	0	4	1	0	0	4	1	40.69	y	N	0
0	0	1	0	1	0	0	0	4	1	0	0	4	1	1.61	y	N	1
1	1	2	0	5	0	0	0	2	0	0	0	2	0	6.5	y	Y	0
2	3	3	0	9	1	0	0	2	0	1	1	3	2	10.5	Y	N	1
0	1	2	0	4	0	0	0	2	0	1	1	3	0	1.18	y	Y	0
1	0	2	0	4	0	0	0	2	0	0	0	2	0	10.1	y	Y	0
1	1	3	0	7	1	0	0	3	0	1	1	4	1	5.05	y	N	1
1	1	2	0	4	0	0	0	2	0	0	0	2	0	2.25	y	Y	0
1	1	1	0	3	0	0	0	4	1	3	1	7	2	22.57	N	N	1
0	0	1	0	2	0	0	0	3	0	1	1	4	1	15.4	Y	N	1
0	1	2	0	3	0	0	0	2	0	0	0	2	0	12.6	y	Y	0
1	1	2	0	5	0	0	0	3	0	2	1	5	1	25.4	y	N	1
1	0	2	0	3	0	0	0	3	0	0	0	3	0	26.8	y	Y	0
0	0	2	0	2	0	0	0	2	0	0	0	2	0	3.19	y	Y	0
1	0	2	0	4	0	0	0	2	0	0	0	2	0	2.97	y	Y	0
1	0	2	0	5	0	0	0	3	0	0	0	3	0	39.67	y	Y	0
1	1	2	0	5	0	0	0	2	0	0	0	2	0	56.2	y	Y	0
2	2	4	0	10	1	0	0	5	1	2	1	7	4	11.12	y	N	2
0	1	2	0	4	0	0	0	2	0	0	0	2	0	1.03	y	Y	0
1	1	2	0	5	0	0	0	4	1	0	0	4	2	5.75	y	N	1
1	2	3	0	7	1	0	0	2	0	0	0	2	0	1.37	N	Y	0
1	0	2	0	3	0	0	0	2	0	1	1	3	0	9.46	y	Y	0
0	1	2	0	3	0	0	0	3	0	0	0	3	0	38.3	y	Y	0
1	1	3	0	7	1	0	0	6	1	1	1	7	3	10.43	y	N	1
1	0	1	0	3	0	0	0	1	0	1	1	2	0	5.93	y	Y	0
2	2	3	0	9	1	0	0	4	1	1	1	5	1	117.98	N	N	1
1	1	2	0	6	0	0	0	2	0	0	0	2	0	5.23	y	Y	0
1	1	2	0	5	0	0	0	2	0	1	1	3	0	25.7	y	Y	0
0	1	2	0	3	0	0	0	3	0	0	0	3	0	11.69	y	Y	0
1	2	3	0	7	1	0	0	1	0	0	0	1	0	14.8	y	Y	0
0	0	1	0	1	0	0	0	2	0	0	0	2	0	23.7	y	Y	0
2	1	2	0	7	0	0	0	6	1	1	1	7	3	21.4	y	N	1
0	0	2	0	2	0	0	0	2	0	0	0	2	0	3	y	Y	0
0	1	2	0	4	0	0	0	5	1	5	2	10	4	21.5	N	N	1
0	0	1	0	1	0	0	0	2	0	1	1	3	1	11.69	y	N	1
1	1	2	0	5	0	0	0	10	3	4	2	14	6	122.5	N	N	2
1	1	2	0	5	0	0	0	2	0	1	1	3	0	15.9	y	Y	0
2	2	3	0	10	1	0	0	3	0	3	1	6	2	13.54	y	N	2
0	0	2	0	2	0	0	0	2	0	1	1	3	1	14.2	y	N	1
0	1	2	0	3	0	0	0	1	0	0	0	1	0	0.45	y	Y	0
0	0	1	0	1	0	0	0	2	0	1	1	3	0	18.49	y	Y	0
1	1	2	0	6	0	0	0	3	0	1	1	4	1	15.43	y	N	1
2	2	2	0	8	0	0	0	2	0	1	1	3	1	0.58	y	N	1
1	2	2	0	6	0	0	0	3	0	0	0	3	1	4.5	y	N	1
1	1	2	0	5	0	0	0	7	2	3	1	10	5	12.47	N	N	2
2	2	3	0	10	1	0	0	4	1	5	2	9	2	23.96	N	N	1
0	1	1	0	2	0	0	0	2	0	0	0	2	0	15.4	y	Y	0
0	2	1	0	5	0	0	0	3	0	0	0	3	0	14.5	y	Y	0
1	2	2	0	7	0	0	0	4	1	6	2	10	6	24.5	N	N	1

					Day 28											Week 8		
SCCAI Urgency of defecation	SCCAI General Well Being	SCCAI EIM	CRP	SCCAI	Stool Freq. during Day	SCCAI Day	Stool freq. during night	SCCAI Night	Total stool	Stools with Blood	SCCAI Amount of blood	SCCAI Urgency of defecation	SCCAI General Well Being	SCCAI EIMs	SCCAI	Stool Freq. during Day	Stool freq. during night	Total stool
0	0	0	5.6	0	2	0	0	0	2	0	0	0	0	0	0	1	0	1
0	1	0	5.12	1	2	0	0	0	2	0	0	0	0	0	0	2	0	2
1	3	0	17	8	-	-	-	-	-	-	-	-	-	-	-	-	-	-
0	2	0	4.56	4	1	0	0	0	1	0	0	0	1	0	1	2	0	2
1	1	0	40.69	3	2	0	0	0	2	0	0	0	0	0	0	2	0	2
0	1	0	1.61	3	2	0	0	0	2	0	0	0	1	0	1	2	0	2
0	2	0	6.5	2	1	0	0	0	1	0	0	0	1	0	1	1	0	1
2	2	0	10.5	6	1	0	0	0	1	0	0	0	0	0	0	2	0	2
1	1	0	1.18	3	2	0	0	0	2	1	1	0	1	0	2	3	0	3
0	1	0	10.1	1	1	0	0	0	1	0	0	0	0	0	0	1	0	1
0	2	0	5.05	4	3	0	0	0	3	0	0	0	1	0	1	2	1	3
0	1	0	2.25	1	2	0	0	0	2	0	0	0	0	0	0	2	0	2
2	3	0	22.57	8	1	0	0	0	1	0	0	0	0	0	0	3	6	9
1	3	0	15.4	6	5	2	1	1	6	1	1	1	2	0	7	3	2	5
1	1	0	12.6	2	3	0	2	1	5	0	0	1	1	0	3	3	1	4
1	1	0	25.4	4	2	0	0	0	2	0	0	0	0	0	0	2	0	2
0	1	0	26.8	1	1	0	0	0	1	0	0	0	1	0	1	2	0	2
0	1	0	3.19	1	2	0	0	0	2	0	0	0	0	0	0	1	0	1
0	1	0	2.97	1	1	0	0	0	1	0	0	0	0	0	0	2	0	2
0	0	0	39.67	0	3	0	0	0	3	1	1	1	1	0	3	3	0	3
0	1	0	56.2	1	2	0	0	0	2	0	0	0	0	0	0	1	0	1
2	3	0	11.12	9	3	0	2	1	5	4	1	1	3	0	6	4	1	5
0	1	0	1.03	1	2	0	0	0	2	0	0	0	0	0	0	2	0	2
1	2	0	5.75	5	3	0	1	1	4	0	0	1	1	0	3	3	2	5
0	2	0	1.37	2	Died	-	-	-	-	-	-	-	-	-	-	Died	-	-
1	1	0	9.46	3	3	0	1	1	4	0	0	1	1	0	3	3	2	5
0	1	0	38.3	1	2	0	0	0	2	0	0	0	0	0	0	2	0	2
0	1	0	10.43	4	2	0	0	0	2	0	0	0	0	0	0	2	0	2
0	1	0	5.93	2	1	0	0	0	1	0	0	0	0	0	0	1	0	1
1	2	0	117.98	6	3	0	1	1	4	0	0	1	1	0	3	3	2	5
0	1	0	5.23	1	2	0	0	0	2	0	0	0	1	0	1	2	0	2
0	2	0	25.7	3	2	0	1	1	3	0	0	0	0	0	1	2	0	2
1	2	0	11.69	3	2	0	0	0	2	0	0	1	2	0	3	2	0	2
1	2	0	14.8	3	1	0	0	0	1	0	0	0	1	0	1	2	0	2
0	0	0	23.7	0	2	0	0	0	2	0	0	0	0	0	0	2	0	2
0	1	0	21.4	4	3	0	1	1	4	0	0	1	1	0	3	3	2	5
0	1	0	3	1	2	0	0	0	2	0	0	0	0	0	0	2	0	2
1	3	0	21.5	8	5	2	1	1	6	1	1	1	2	0	7	4	4	8
0	1	0	11.69	3	3	0	1	1	4	0	0	0	2	0	3	2	0	2
2	4	0	122.5	13	Died	-	-	-	-	-	-	-	-	-	-	Died	-	-
0	2	0	15.9	3	3	0	0	0	3	0	0	1	1	0	2	3	0	3
2	3	0	13.54	8	LTFU	-	-	-	-	-	-	-	-	-	-	LTFU	-	-
0	1	0	14.2	3	1	0	0	0	1	0	0	0	1	0	1	2	0	2
0	1	0	0.45	1	2	0	1	1	3	0	0	0	1	0	2	3	2	5
0	0	0	18.49	1	2	0	1	1	3	0	0	0	0	0	1	2	0	2
1	2	0	15.43	5	2	0	0	0	2	0	0	0	1	0	1	2	0	2
1	2	0	0.58	5	2	0	0	0	2	0	0	0	1	0	1	3	0	3
1	2	0	4.5	4	1	0	0	0	1	0	0	0	0	0	0	1	-	1
2	4	0	12.47	11	4	2	0	0	4	3	2	3	2	0	9	4	5	9
2	2	0	23.96	8	4	2	0	0	4	4	1	2	2	0	7	4	3	7
1	1	0	15.4	2	2	0	1	1	3	0	0	1	1	0	3	3	1	4
1	1	0	14.5	2	2	0	0	0	2	0	0	0	1	0	1	LTFU	-	-
1	3	0	24.5	8	6	2	4	2	10	5	2	2	4	0	12	3	0	3

				Death		Rescue Therapy			Survival Analysis										
Stools with Blood	SCCAI General Well Being	MAYO SCORE	CLINICAL REMISSION	Expired	Expired Day	Rescue Therapy	Which Rescue Therapy	Day on which Rescue Therapy Given	Event (rescue therapy or colectomy)	Time	Censor	Facial edema	Venous Thromboembolism	Arthralgia	Hairfall	Acne	LVF	Pruritus	URTI
0	0	1	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	0	2	Y	-	-	-	-	-	-	90	-	y	-	-	-	-	-	-	-
-	-	-	N	-	-	Y	IFX	7	1	7	-	-	-	-	-	-	-	-	-
0	1	1	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	0	1	Y	-	-	-	-	-	-	90	-	y	-	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	y	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	y	-	-	-	-	-
0	1	1	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
2	2	5	N	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	-	-	-	y	y	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
4	3	8	N	-	-	y	IFX	7	1	28	-	-	-	-	-	-	-	-	-
3	2	6	N	-	-	-	-	-	-	90	-	-	-	-	-	-	y	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	-	-	-	y	-	-	y	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	y	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	-	y	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	y	-	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
3	3	7	N	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
1	1	3	N	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	3	N	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
-	-	-	N	y	28	-	-	-	-	56	1	-	-	-	-	-	-	-	-
0	1	3	N	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	0	2	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	y	-	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	1	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
2	2	6	N	-	-	y	IFX	7	1	56	-	-	-	-	y	-	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	-	-	-	y	y	-	-	-
-	-	-	N	y	14	y	colectomy	7	-	14	1	-	-	-	-	-	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
-	-	-	N	-	-	-	-	-	-	7	1	-	-	-	-	-	-	-	-
0	1	1	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	2	Y	-	-	-	-	-	-	90	-	-	-	-	y	-	-	-	y
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	1	1	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
1	2	4	N	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
0	0	0	Y	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
4	4	8	N	-	-	y	IFX	7	1	80	-	-	-	-	-	-	-	-	-
2	2	7	N	-	-	Y	IFX	7	1	7	-	-	-	-	-	-	-	-	-
2	1	4	N	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-
-	-	-	N	-	-	-	-	-	-	28	1	-	-	-	-	-	-	-	-
1	1	3	N	-	-	Y	IFX	57	1	8	-	-	-	-	-	-	-	-	-

Comments														
-	Hemoglobin	MCV	Neutrophils	Lymphocytes	NLR	Platelt Count	FBS	ESR	CRP	CRA	Fecal Calprotectin	Total cholestrol	LDL	HDL
-	12.9	89.4	8385	3870	2.166666667	151	243	32	109.13	34.8658147	>2000	112	56	44
-	10.8	73	12400	1808	6.85840708	406	110	29	110	32.93413174	>2000	89	42	30
-	12.9	81.8	9224	2052	4.495126706	464	105	34	8.77	1.957589286	>2000	154	111	31
-	9.1	83.3	3797	1643	2.311016433	373	103	30	44.4	19.05579399	>2000	126	50	35
-	7.3	63	9100	1663	5.472038485	321	109	28	62.15	17.07417582	>2000	150	89	38
DURAL VENOUS THROMBOSIS AND HEMORRHAGIC VENOUS INFARCT LEFT TEMPORAL LOBE WITH SEIZURE	6.6	82.4	3888	545	7.133944954	493	110	12	63.73	49.02307692	>2000	56	23	16
-	6.9	79.6	4599	1825	2.52	207	98	58	26.75	13.1773399	>2000	76	39	26
-	10	82.8	5529	2328	2.375	370	110	36	67.29	19.79117647	>2000	154	111	31
-	11.8	78.2	6741.5	1920.6	3.51010101	395	104	15	18.31	7.504098361	>2000	60	30	25
-	12	72.5	7127.6	2132.1	3.342995169	188	110	37	62.72	17.71751412	>2000	87	51	32
-	6.7	79.7	6479.2	1783.6	3.632653061	350	96	16	60	36.58536585	>2000	110	56	26
-	12.9	85	13550	1538.6	8.806707396	242	82	32	4.94	1.563291139	>2000	131	80	43
-	11.5	88.4	2511.6	2090.4	1.201492537	274	140	36	45.45	12.35054348	>2000	124	82	37
-	10.1	80.3	5170	3403	1.519247723	325	109	39	6.4	2.098360656	>2000	120	74	36
-	6.2	53.3	6902	2760.8	2.5	526	101	29	70.84	21.02077151	>2000	132	76	36
-	10.9	76.2	9984	1274	7.836734694	342	126	17	6.75	1.537585421	>2000	170	94	69
BILATERAL RETINAL VEIN OCCLUSION	12.8	88.4	5512.5	1740	3.168103448	253	110	12	12.36	3.252631579	>2000	118	73	34
-	8.1	62.2	5052	1039	4.862367661	445	120	26	62.3	22.01413428	>2000	72	33	17
-	5.7	59.4	3709	1690	2.194674556	333	110	50	4.96	1.401129944	>2000	110	96	40
-	10.4	71.8	10067	1613	6.24116553	443	116	45	16.5	6.547619048	>2000	110	79	26
-	13.5	74.3	5664	1962	2.886850153	320	86	47	19.78	5.993939394	>2000	150	91	36
-	4.4	60.2	7213	1040	6.935576923	313	109	36	77.21	23.3969697	>2000	95	53	35
-	7.9	80	4635	1112	4.168165468	375	107	62	13.41	4.841155235	>2000	156	109	40
-	11	84.8	13872	1598	8.680851064	497	110	60	202.58	63.50470219	>2000	134	78	41
-	9.1	95.6	3272	620	5.277419355	140	120	2	13.55	5.765957447	>2000	64	31	30
-	9.4	82.3	4943	2055	2.405352798	346	119	102	95.03	39.26859504	>2000	104	67	29
-	10.5	83.9	9462.5	1950	4.852564103	379	106	69	160.08	52.65789474	>2000	107	60	24
-	13.5	84.6	7630	2180	3.5	386	94	22	47.96	15.72459016	>2000	108	72	29
-	12.4	92.1	5161	634	8.140378549	282	110	-	75.48	22.46428571	>2000	137	79	96
-	10.7	82.1	13720	3220	4.260869565	476	75	77	180.97	51.70571429	>2000	72	40	27
-	4.1	68	11160	2101	5.311756307	517	102	24	47.37	23.685	1063	112	74	29
-	10.3	83.7	6143	3213	1.911920324	306	102	26	3.83	1.072829132	>2000	136	67	51
-	10.5	80	3879	4285	0.905250875	150	105	14	26.44	6.371084337	>2000	-	-	-
-	9.8	86.8	5921	1369	4.325054785	303	90	32	54.11	16.96238245	>2000	126	79	41
-	11.4	91.8	12972	400	32.43	334	92	39	62.56	18.78678679	>2000	134	78	41
-	11	80.6	5709	602	9.483388704	293	99	45	14.25	3.720626632	>2000	220	138	72
-	10.1	68	6541	1739	3.761357102	448	77	57	11.83	2.549568966	>2000	109	65	39
-	9.7	94.1	4409	1762	2.502270148	209	105	6	0.43	0.099537037	>2000	98	56	19
-	6.7	63.7	8943.6	1624	5.507142857	699	101	125	143.03	46.74183007	>2000	204	136	54
-	8.3	83.6	6936	1122	6.181818182	699	101	85	44	22	>2000	63	29	27
-	6.4	63.1	6459	1402	4.606990014	264	112	2	41.52	29.44680851	>2000	119	67	32
-	9.2	83.7	1677	632	2.653481013	241	103	58	160.41	81.84183673	>2000	-	-	-
-	9	68.2	4420	2187	2.021033379	416	109	39	4.67	1.122596154	>2000	139	82	42
-	4.4	60.6	9984	3260	3.062576687	931	70	70	26.96	10.4496124	>2000	90	47	33
-	9.2	103.1	2765	630	4.388888889	60	102	70	227.2	108.1904762	>2000	132	82	34
-	7.6	64.8	9570	2030	4.714285714	568	95	29	49.21	21.6784141	>2000	142	88	25
-	9.4	74.7	13433	3798	3.536861506	412	119	61	23.89	7.560126582	>2000	132	90	40
-	9.8	79.3	6990	2640	2.647727273	444	-	-	84.91	29.68881119	-	-	-	-
-	8.9	64.4	8400	1030	8.155339806	446	-	-	8.32	1.90389016	-	-	-	-
-	9.2	77.3	7000	1800	3.888888889	632	-	-	114.65	36.05345912	-	-	-	-
-	8.9	69.5	8200	2130	3.849765258	193	95	45	43.04	12.80952381	>2000	87	47	30
-	11	78.5	6210	2230	2.784753363	367	96	12	122.3	47.40310078	>2000	-	-	-
-	6.7	62.3	7800	1600	4.875	350	96	16	60	36.58536585	>2000	110	56	26

Investigations Day 0																			
Triglyceride	Total Bilirubin	Direct Bilirubin	ALT	AST	ALP	Total Protein	Albumin	Urea	Creatinine	HBsAg	Anti-HCV	CMV(inclusion bodies)	CMV(IHC)	EBER	Mantoux	GDH	Toxin A	Toxin B	Chest X ray
102	0.68	0.09	12	20	48	5.8	3.13	30	0.58	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
83	0.55	0.12	61	24	109	6.8	3.34	38	0.6	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
321	1.24	0.5	17	16	116	8.4	4.48	26	1.02	NEG	NEG	NEG	NEG	1	-	-	-	-	-
164	0.28	0.03	12	32	130	5	2.33	35	0.8	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
101	0.29	0.16	19	19	75	6.1	3.64	15	0.82	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
84	0.1	0.06	11	11	135	3.4	1.3	13	0.4	NEG	NEG	NEG	POSITIVE	-	NEG	NEG	NEG	NEG	WNL
58	0.53	0.05	11	47	78	5.3	2.03	14	0.95	NEG	NEG	-	POSITIVE	-	NEG	NEG	NEG	NEG	WNL
321	0.47	0.09	37	22	81	5.7	3.4	14	0.58	NEG	NEG	NEG	POSITIVE	-	NEG	NEG	NEG	NEG	WNL
72	0.4	0.09	33	24	83	5.5	2.44	10	0.49	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
57	1.06	0.38	20	22	120	6.9	3.54	14	0.87	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
103	0.36	0.25	10	13	104	4.7	1.64	28	1.49	NEG	NEG	POSITIVE	POSITIVE	-	NEG	NEG	NEG	NEG	WNL
60	0.4	0.08	25	13	71	6.1	3.16	32	0.67	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
64	0.37	0.14	34	30	161	7.4	3.68	19	0.86	NEG	NEG	POSITIVE	NEGATIVE	-	NEGATIVE	NEG	NEG	NEG	WNL
91	0.75	0.28	6	15	96	6.5	3.05	10	0.86	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
135	0.24	0.09	7	12	77	6.8	3.37	19	0.65	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
69	0.51	0.16	21	23	144	7.1	4.39	15	1.09	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
71	0.48	0.1	19	17	84	6.5	3.8	17	0.84	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
95	0.4	0.3	121	116	104	6.2	2.83	17	0.77	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
140	0.95	0.21	17	22	76	6.3	3.54	18	0.6	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
118	0.43	0.13	13	22	66	5.4	2.52	11	0.31	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
163	0.18	0.08	17	12	133	6.6	3.3	18	0.79	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
94	0.43	0.08	6	18	42	6.2	3.3	12	0.41	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
118	0.24	0.04	8	18	60	5.2	2.77	10	0.47	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
152	0.42	0.24	4	9	72	6.2	3.19	10	0.56	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
59	0.83	0.24	22	23	342	4.4	2.35	19	0.62	NEG	NEG	NEG	POSITIVE	-	NEG	NEG	NEG	NEG	WNL
106	0.44	0.1	192	24	163	5.3	2.42	20	0.42	NEG	NEG	NEG	POSITIVE	-	NEG	NEG	NEG	NEG	WNL
128	0.33	0.15	22	18	215	6.9	3.04	28	1.55	NEG	NEG	NEG	NEG	-	NEG	POS	NEG	NEG	WNL
102	0.8	0.4	40	42	110	7.4	3.05	20	0.81	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
42	0.44	0.24	14	30	161	8.4	3.36	21	0.63	NEG	NEG	NEG	POSITIVE	-	NEG	NEG	NEG	NEG	WNL
52	0.29	0.16	15	15	107	6.5	3.5	12	0.71	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
102	0.21	0.03	9	15	121	5.1	2	14	0.66	NEG	NEG	NEG	NEG	3	NEG	POS	POS	POS	WNL
90	0.26	0.1	47	49	60	6.8	3.57	21	0.78	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
-	0.39	0.1	90	44	127	6.3	4.15	23	0.6	NEG	NEG	NEG	NEG	11	NEG	NEG	POS	POS	WNL
84	0.15	0.05	10	13	80	5.8	3.19	24	0.96	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
152	0.47	0.08	10	11	74	6.1	3.33	69	1.02	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
118	1.13	0.34	25	23	105	6.4	3.83	25	0.94	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
64	0.52	0.22	16	24	73	8.3	4.64	22	0.68	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
97	0.34	0.16	13	19	64	7.1	4.32	17	0.53	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
66	0.35	0.24	69	26	186	6.8	3.06	11	0.42	NEG	POSITIVE	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
75	0.35	0.08	10	16	83	4.2	2	41	0.9	NEG	NEG	NEG	POSITIVE	-	NEG	NEG	NEG	NEG	WNL
65	0.16	0.05	10	8	33	2.9	1.41	6	0.28	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	WNL	WNL
-	0.78	0.3	16	33	78	3.8	1.96	12	0.37	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
151	0.35	0.11	10	17	66	7.5	4.16	11	0.63	NEG	POSITIVE	NEG	-	-	NEG	NEG	NEG	NEG	WNL
63	0.37	0.1	8	15	70	6.2	2.58	13	0.44	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
163	1.33	0.28	13	30	46	5.2	2.1	16	0.58	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
124	0.29	0.06	16	34	98	5.2	2.27	20	0.75	NEG	NEG	NEG	NEG	3	NEG	POS	POS	POS	WNL
71	0.28	0.12	17	24	96	6.4	3.16	9	0.77	NEG	NEG	NEG	NEG	NEG	POSITIVE	POSITIVE	POSITIVE	WNL	119
-	0.43	0.09	16	17	69	5.9	2.86	13	0.77	NEG	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	-
-	0.33	0.15	27	53	81	7	4.37	20	0.71	-	-	-	-	-	-	NEG	NEG	NEG	-
-	0.26	0.11	9	6	80	6.4	3.18	15	0.7	NEG	NEG	NEG	POSITIVE	8	NEG	NEG	NEG	NEG	-
140	-	-	31	36	83	-	3.36	18	0.88	NEG	NEG	NEG	NEG	NEG	NEG	NEG	POSITIVE	NEG	NORMAL
-	-	-	6	44	232	-	2.58	8	0.92	NEG	NEG	NEG	NEG	3	NEG	POSITIVE	NEG	NEG	NORMAL
103	-	-	13	10	104	-	1.64	28	1.49	NEG	NEG	POSITIVE	POSITIVE	5	NEG	POSITIVE	POSITIVE	POSITIVE	NORMAL

					Duration of Stay				Previous treatment			Day 0		treatment at discharge				
Group	Intials	Age	Sex	MRD	number of days in ward	number of days in ICU	TOTAL STAY IN HOSPITAL	Previous flares	Previous use of steroids	Previous AZA	Previous anti-TNFs	baseline HR	baseline temperature	5-ASA	Thiopurines	Steroids	Tofacitinib	IFX
2	JPJ	74	MALE	1274294	19	4	23	Multiple	YES	YES	NO	88	98	NO	NO	YES	NO	NO
2	S	48	FEMALE	1029295	7	0	7	2	YES	NO	NO	102	98.4	YES	YES	YES	NO	NO
2	G	35	MALE	720747	7	0	7	0	YES	NO	NO	84	98.2	YES	NO	YES	NO	YES
2	KR	42	FEMALE	1184158	9	0	9	2	YES	NO	NO	82	97.6	YES	NO	YES	NO	NO
2	AK	34	FEMALE	1184024	13	0	13	0	NO	NO	NO	104	98.8	YES	NO	YES	NO	NO
2	S	31	FEMALE	1163295	19	0	19	0	YES	NO	NO	124	99.1	YES	NO	YES	NO	YES
2	ML	56	MALE	1125186	10	3	13	0	YES	NO	NO	103	96.9	EXPIRE	EXPIRE	EXPIRE	EXPIRE	EXPIRE
2	JK	35	FEMALE	1326036	10	0	10	0	NO	NO	NO	80	97	YES	NO	YES	NO	NO
2	GS	38	MALE	1370897	8	0	8	0	NO	NO	NO	72	99.8	YES	NO	YES	NO	NO
2	NK	21	FEMALE	1360864	9	0	9	0	NO	NO	NO	97.2	100	YES	NO	YES	NO	NO
2	TK	73	FEMALE	1359613	10	0	10	0	NO	NO	NO	80	98.8	YES	NO	YES	NO	NO
2	GS	45	MALE	1369793	19	0	19	0	YES	NO	NO	62	99.6	NO	YES	YES	NO	NO
2	PS	60	MALE	1282855	6	0	6	0	NO	NO	NO	72	98.2	YES	NO	YES	NO	NO
2	SS	42	MALE	904113	7	0	7	0	YES	NO	NO	112	99	YES	NO	YES	NO	NO
2	BS	44	MALE	809825	7	0	7	0	YES	NO	NO	107	98	YES	YES	YES	NO	NO
2	AS	37	MALE	1302374	9	0	9	0	NO	NO	NO	100	99.8	YES	YES	YES	NO	NO
2	AD	27	MALE	1238230	7	0	7	-	NO	NO	NO	90	98.6	YES	NO	YES	NO	NO
2	SK	38	FEMALE	1311730	0	3	3	0	YES	NO	NO	112	98.2	EXPIRE	EXPIRE	EXPIRE	EXPIRE	EXPIRE
2	SK	18	FEMALE	1317619	7	0	7	0	YES	NO	NO	84	98	YES	NO	YES	NO	NO
2	KS	25	MALE	1130486	9	0	9	0	YES	NO	NO	102	98	YES	NO	YES	NO	YES
2	MK	18	FEMALE	1165598	23	9	32	0	YES	NO	NO	130	98.3	EXPIRE	EXPIRE	EXPIRE	EXPIRE	EXPIRE
2	MK	42	FEMALE	1195322	16	7	23	3	YES	NO	NO	140	98.9	EXPIRE	EXPIRE	EXPIRE	EXPIRE	EXPIRE
2	VJ	42	FEMALE	1136976	5	0	5	0	NO	NO	NO	104	98.6	YES	NO	YES	NO	NO
2	KS	52	MALE	1343210	10	0	10	0	NO	NO	NO	74	97.4	YES	NO	YES	NO	NO
2	GS	27	MALE	1333023	5	0	5	0	YES	NO	NO	104	98.2	YES	NO	YES	NO	NO
2	NK	64	MALE	1355801	14	0	14	-	NO	NO	NO	85	99.2	-	-	-	-	-
2	SSM	45	MALE	1308836	9	0	9	0	NO	NO	NO	80	97.4	YES	NO	YES	NO	NO
2	SS	18	MALE	1306675	6	0	6	0	YES	NO	NO	82	98	YES	NO	YES	NO	NO
2	MS	40	MALE	1194396	7	0	7	0	YES	NO	NO	76	98.8	YES	YES	YES	NO	NO
2	SS	43	MALE	1304346	5	0	5	0	NO	NO	NO	110	97.2	YES	NO	YES	NO	NO
2	DRG	57	MALE	1130623	7	0	7	0	NO	NO	NO	58	96.2	YES	NO	YES	NO	NO
2	MK	36	MALE	1166276	8	0	8	-	NO	NO	NO	65	98.7	-	-	-	-	-
2	RK	26	FEMALE	1277028	5	0	5	-	NO	NO	NO	101	98.6	-	-	-	-	-
2	SD	60	FEMALE	423633	24	3	27	Multiple	YES	YES	YES	104	98	-	-	-	-	-
2	AK	63	MALE	1275816	7	0	7	-	NO	NO	NO	124	99.4	-	-	-	-	-
2	KK	48	MALE	811145	12	0	12	3	YES	YES	NO	96	97.4	YES	YES	YES	NO	NO
2	BS	72	MALE	1326080	6	0	6	-	NO	NO	NO	125	98.7	-	-	-	-	-
2	PR	45	FEMALE	1324673	5	0	5	-	NO	NO	NO	107	96.4	-	-	-	-	-
2	TK	35	FEMALE	1328157	6	0	6	-	NO	NO	NO	96	98.7	-	-	-	-	-
2	PK	28	MALE	791075	5	0	5	-	NO	NO	NO	94	99.2	-	-	-	-	-
2	MK	31	FEMALE	1337383	6	0	6	0	NO	NO	NO	98	98	-	-	-	-	-
2	HK	31	FEMALE	1337900	15	0	15	15	YES	YES	NO	78	97.8	YES	NO	YES	NO	YES
2	SS	29	MALE	1363465	5	0	5	-	NO	NO	NO	67	100.2	-	-	-	-	-
2	BM	26	MALE	1378913	7	0	7	1	YES	NO	NO	86	98.2	YES	YES	YES	NO	NO
2	SK	46	FEMALE	1302418	9	0	9	-	NO	NO	NO	61	99.5	-	-	-	-	-
2	KG	62	FEMALE	1405242	13	0	13	-	NO	NO	NO	72	98.2	-	-	-	-	-
2	Gs	35	MALE	1266863	13	0	13	3	YES	YES	NO	98	98	YES	YES	YES	NO	YES
2	GS	24	MALE	960581	6	0	6	0	YES	NO	NO	82	98.1	YES	YES	YES	NO	NO
2	AS	20	MALE	1409793	7	0	7	0	YES	NO	NO	74	98	YES	NO	YES	NO	NO
2	GSS	37	MALE	1172110	13	0	13	-	NO	NO	NO	58	98.1	-	-	-	-	-
2	HK	42	FEMALE	841069	11	0	11	3	YES	YES	YES	95	98	YES	YES	YES	NO	NO

		Addictions				comorbidities												
Year of Diagnosis	Disease Duration	Alcohol	Smoking	Opium	IVDU	Diabetes	Hypertension	Hypothyroidism	CAD	COAD	Others	Chicken Pox	Shingles	Weight	Height inches	Ht in m	BMI	Stool Freq. during Day
2008	15	-	-	-	-	-	-	-	-	-	-	-	-	68	67	1.7018	23.4796638	5
2013	10	-	-	-	-	-	-	-	-	-	-	-	-	62	61	1.5494	25.82644241	6
2017	6	-	-	-	-	-	-	-	-	-	-	-	-	52	59	1.4986	23.15431232	6
2019	4	-	-	-	-	-	-	-	-	-	-	-	-	50	62	1.5748	20.16133065	3
2019	4	-	-	-	-	-	-	-	-	-	-	-	-	53	62	1.5748	21.37101048	6
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	43	58	1.4732	19.81276257	8
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	64	71	1.8034	19.67867455	4
2022	1	-	-	-	-	-	Y	-	-	-	-	-	-	48	62	1.5748	19.35487742	4
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	69.8	74	1.8796	19.7571615	8
2022	1	-	-	-	-	-	-	-	-	-	ASTHMA,ARTHRITIS	Y	-	51	61	1.5494	21.24433166	4
2022	1	-	-	-	-	-	Y	-	-	-	ARTHRITIS, ILD	-	Y	56	58	1.4732	25.80266754	6
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	64.3	68	1.7272	21.55389259	8
2022	1	Y	-	-	-	-	-	-	-	-	-	-	-	60	67	1.7018	20.71735041	5
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	67	68	1.7272	22.45895495	7
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	75	64	1.6256	28.38140442	6
2022	1	Y	-	Y	-	-	-	-	-	-	-	-	-	79	70	1.778	24.9898459	7
2019	4	-	-	-	-	-	-	-	-	-	Epilepsy and NSAIDs use	-	-	71	65	1.651	26.04738937	5
2017	6	-	-	-	-	-	-	-	-	-	-	-	-	40	62	1.5748	16.12906452	6
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	35	62	1.5748	14.11293145	6
2020	3	-	-	-	-	-	-	-	-	-	-	-	-	60	71	1.8034	18.44875739	6
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	29	52	1.3208	16.62355396	4
2018	5	-	-	-	-	-	-	-	-	-	-	-	-	25	48	1.2192	16.81861003	6
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	42	61	1.5494	17.49533195	10
2022	1	Y	-	-	-	-	-	-	-	-	-	Y	-	49	66	1.6764	17.43575572	6
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	71.2	69	1.7526	23.18005056	6
2020	3	-	-	-	-	-	-	-	-	-	-	-	-	49.68	65	1.651	18.22583527	10
2022	1	Y	-	Y	-	-	-	-	-	-	-	-	-	58	65	1.651	21.27814907	4
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	56	69	1.7526	18.23150044	4
2022	1	Y	-	-	-	Y	-	-	-	-	-	-	-	80	66	1.6764	28.46653995	8
2021	2	Y	-	Y	-	-	-	-	-	-	-	-	-	75	69	1.7526	24.41718809	5
2021	2	-	-	Y	-	-	Y	-	Y	-	-	-	-	52	60	1.524	22.38893367	6
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	54	62	1.5748	21.7742371	7
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	57	61	1.5494	23.74366479	6
2013	10	-	-	-	-	-	-	-	-	-	-	-	Y	55	61	1.5494	22.91055375	9
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	53	60	1.524	22.81949008	7
2019	4	-	-	-	-	-	-	-	-	-	-	Y	-	51	65	1.651	18.71009659	6
2002	21	-	-	-	-	-	-	-	-	-	-	-	-	50	66	1.6764	17.79158747	8
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	52	62	1.5748	20.96778387	6
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	51	62	1.5748	20.56455726	7
2016	7	-	-	-	-	-	-	-	-	-	-	-	-	45	65	1.651	16.50890876	6
2022	1	-	-	-	-	-	-	Y	-	-	-	Y	-	55.5	64	1.6256	21.00223927	7
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	49	66	1.6764	17.43575572	7
2018	5	-	-	-	-	-	-	-	-	-	-	-	-	46	58	1.4732	21.19504834	7
2021	2	-	-	-	-	-	-	-	-	-	-	Y	-	65	66	1.6764	23.12906371	15
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	58	59	1.4986	25.82596375	6
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	52	60	1.524	22.38893367	6
2019	4	-	-	-	-	-	-	-	-	-	-	-	-	65	68	1.7272	21.78853839	5
2020	3	-	-	-	-	-	-	-	-	-	-	-	-	82	61	1.5494	34.15755286	6
2022	1	-	-	-	-	-	-	-	-	-	-	-	-	49.8	67	1.7018	17.19540084	8
2021	2	-	-	-	-	-	-	-	-	-	-	-	-	60	60	1.524	25.833385	7
2019	4	-	-	-	-	-	-	-	-	-	AS(16)	Y	-	81.4	62	1.5748	32.82264629	10

Day 0																	
SCCAI Score Day	Stool freq. during night	SCCAI Score Night	Total stool	Stools with Blood	SCCAI Amount of blood	SCCAI Urgency of defecation	SCCAI General Well Being	SCCAI EIMs	Endo Mayo	SCCAI	Partial Mayo	Total Mayo	Abdominal Pain	Abdominal Tenderness	Need for anti diarrheal drugs	Stool Freq. during Day	SCCAI Day
1	5	2	10	6	2	3	4	0	2	12	9	11	2	1	0	4	1
1	3	1	9	6	2	2	3	0	2	9	9	11	1	0	0	2	0
1	3	1	9	6	2	2	3	0	2	9	9	11	1	0	0	4	1
0	3	1	6	6	3	3	2	0	3	9	8	11	1	0	0	1	0
1	2	1	8	6	2	2	3	0	2	9	9	11	1	0	0	4	1
2	6	2	14	14	3	3	4	0	3	14	9	12	1	0	0	8	2
1	3	1	7	6	2	3	4	0	2	11	9	11	2	1	0	6	1
1	2	1	6	6	2	1	4	0	2	9	9	11	1	0	0	3	0
2	7	2	15	15	3	2	4	0	2	13	9	11	2	1	0	5	1
1	2	1	6	6	3	2	4	0	3	11	9	12	2	1	0	4	1
1	4	2	10	6	2	2	3	0	3	10	9	12	1	0	0	3	0
2	3	1	11	11	2	2	3	0	3	10	9	12	1	0	0	5	1
1	3	1	8	6	3	2	2	0	2	9	8	10	1	0	0	2	0
2	5	2	12	6	2	1	4	0	2	11	9	11	2	1	0	4	1
1	2	1	8	6	2	1	3	0	2	8	9	11	1	0	0	6	1
2	4	2	11	6	2	2	4	0	3	12	9	12	2	1	0	3	0
1	3	1	8	6	3	1	3	0	2	9	9	11	1	0	0	6	1
1	4	2	10	10	2	3	4	0	3	12	9	12	2	1	0	Death	-
1	4	2	10	9	2	3	4	0	3	12	9	12	2	1	0	6	1
1	4	2	10	10	3	2	4	0	3	12	9	12	2	1	0	4	1
1	3	1	7	7	3	3	4	0	3	12	9	12	3	2	0	6	1
1	3	1	9	7	3	3	4	0	3	12	8	11	3	2	0	6	1
3	6	2	16	6	2	2	4	0	2	13	9	11	3	1	1	2	0
1	4	2	10	6	2	3	3	0	3	11	9	12	1	0	0	6	1
1	1	1	7	6	3	3	2	0	2	10	8	10	1	0	0	1	0
3	6	2	16	16	3	3	4	0	3	15	9	12	3	1	1	9	2
1	4	2	8	6	2	2	3	0	3	10	9	12	1	0	0	3	0
1	2	1	6	6	3	1	2	0	3	8	8	11	2	0	0	3	0
2	2	1	10	6	1	2	3	0	2	9	8	10	1	0	0	6	2
1	2	1	7	6	2	1	3	0	2	8	9	11	1	0	0	2	0
1	3	1	9	6	3	1	2	0	3	8	8	11	1	0	0	6	1
3	3	1	10	6	2	2	3	0	3	11	9	12	1	0	0	1	0
1	3	1	9	6	1	3	3	0	3	9	8	11	1	0	0	1	0
2	4	2	13	6	2	2	3	0	3	11	9	12	1	0	0	6	1
2	3	1	10	6	1	2	3	0	3	9	8	11	1	0	0	1	0
1	10	2	16	8	2	3	3	0	3	11	8	11	1	0	1	4	1
2	2	1	10	6	0	3	3	0	3	9	8	11	1	0	0	1	0
1	3	1	9	6	2	2	3	0	3	9	9	12	2	1	0	3	0
2	3	1	10	6	1	2	3	0	3	9	9	12	2	1	0	2	0
1	4	2	10	6	2	2	4	0	3	11	9	12	3	1	0	1	0
2	3	1	10	6	2	2	3	0	3	10	9	12	2	1	0	DISCHARGE	-
2	5	2	12	12	3	3	4	0	3	14	9	12	3	1	0	7	2
2	4	2	11	6	1	2	4	0	3	11	9	12	2	1	0	1	0
3	5	2	20	6	2	2	3	0	3	12	9	12	2	1	1	6	1
1	4	2	10	6	2	3	4	0	3	12	9	12	2	1	0	2	0
1	2	1	8	6	3	3	4	0	3	12	8	11	2	1	0	5	1
1	1	1	6	6	3	3	3	0	3	11	9	12	2	1	0	4	1
1	2	1	8	6	2	3	3	0	2	10	8	10	1	0	0	3	0
2	7	2	15	15	3	3	3	0	3	13	9	12	1	0	1	2	0
2	2	1	9	6	3	3	4	0	3	13	8	11	3	1	0	6	1
3	10	2	20	7	2	3	4	0	3	14	8	11	3	1	1	10	3

Day 3																
Stool freq. during night	SCCAI Night	Total stool	CRP	Response at Day 3 Oxford criteria	Stools with Blood	SCCAI Amount of blood	SCCAI Urgency of defecation	SCCAI General Well Being	SCCAI EIMs	SCCAI	Abdominal Pain	Abdominal Tenderness	Need for anti diarrheal drugs	Lichtiger Total Stools	Lichtiger Blood	Lichtiger nocturnal stools
3	1	7	11.45	Y	4	2	3	4	0	11	0	0	0	3	2	1
0	0	2	3.92	Y	0	0	1	2	0	3	0	0	0	0	0	0
2	1	6	55.61	N	3	2	1	2	0	7	0	0	0	2	2	1
1	1	2	11.2	Y	1	1	1	1	0	4	0	0	0	0	1	1
2	1	6	48.66	N	2	1	1	2	0	6	0	0	0	2	1	1
6	2	14	54.53	N	14	2	3	4	0	13	1	0	1	4	2	1
3	1	9	92.36	N	6	2	2	4	0	10	1	0	0	3	2	1
1	1	4	1.21	Y	1	1	1	2	0	5	0	0	0	1	1	1
4	2	9	34.28	N	5	0	0	4	0	7	1	0	0	3	0	1
2	1	6	155.19	N	4	2	2	3	0	9	1	0	0	2	2	1
3	1	6	49.87	N	1	1	2	3	0	7	1	0	0	2	1	1
5	2	10	3.26	N	7	2	2	3	0	10	1	0	1	4	2	1
0	0	2	7.24	Y	0	0	1	1	0	2	0	0	0	0	0	0
1	1	5	11.97	Y	2	1	1	3	0	7	1	0	0	2	1	1
2	1	8	1.67	Y	3	2	1	3	0	8	1	0	0	3	2	1
1	1	4	8.8	Y	2	1	2	3	0	7	1	0	0	1	1	1
2	1	8	46.6	N	3	2	1	3	0	8	1	0	0	3	2	1
-	-	-	-	N	-	-	-	-	-	-	-	-	-	-	-	-
3	1	9	30.68	N	6	2	3	4	0	11	1	0	0	3	2	1
4	2	8	79	N	6	3	2	4	0	12	1	0	0	3	3	1
3	1	9	138.86	N	6	3	3	4	0	12	1	0	0	3	3	1
3	1	9	60.4	N	4	3	2	4	0	11	1	0	0	3	3	1
0	0	2	1.08	Y	0	0	1	3	0	4	1	0	0	0	0	0
1	1	7	1.2	Y	5	3	2	3	0	10	1	0	0	3	3	1
1	1	2	32.68	Y	1	1	1	2	0	5	0	0	0	0	1	1
3	1	12	77.9	N	8	2	2	3	0	10	1	0	1	4	2	1
3	1	6	45.58	Y	2	1	2	3	0	7	1	0	0	2	1	1
0	0	3	7.5	Y	0	0	1	2	0	3	0	0	0	1	0	0
2	1	8	0.1	Y	3	2	1	3	0	9	1	0	0	3	2	1
0	0	2	12.4	Y	0	0	0	1	0	1	0	0	0	0	0	0
3	1	9	18.2	N	0	0	0	2	0	4	0	0	0	3	0	1
1	1	2	0.8	Y	0	0	0	2	0	3	0	0	0	0	0	1
1	1	2	0.95	Y	1	1	0	2	0	4	0	0	0	0	1	1
3	1	9	41.96	N	0	0	3	3	0	8	1	0	0	3	0	1
1	1	2	1.58	Y	0	0	0	2	0	3	0	0	0	0	0	1
9	2	13	25.66	N	3	2	3	3	0	11	1	0	1	4	2	1
3	1	4	6.47	Y	0	0	0	2	0	3	0	0	0	1	0	1
1	1	4	16.78	Y	1	1	0	2	0	4	0	0	0	1	1	1
1	1	3	26.45	Y	0	0	0	2	0	3	0	0	0	1	0	1
0	0	1	12.4	Y	0	0	0	2	0	2	0	0	0	0	0	0
-	-	4	14.36	Y	-	-	-	-	-	-	-	-	-	-	-	-
3	1	10	60.73	N	7	3	3	4	0	13	1	0	1	4	3	1
0	0	1	25.4	Y	0	0	0	2	0	2	0	0	0	0	0	0
2	1	8	16.8	Y	2	1	2	3	0	8	1	0	0	3	1	1
0	0	2	21	Y	0	0	0	2	0	2	0	0	0	0	0	0
1	1	6	2.14	Y	0	0	0	2	0	4	0	0	0	2	0	1
1	1	5	93.68	N	5	3	3	3	0	11	1	0	0	2	3	1
1	1	4	31.32	Y	0	0	1	1	0	3	0	0	0	1	0	1
1	1	3	41.27	Y	0	0	1	2	0	4	0	0	0	1	0	1
2	1	8	2.65	Y	0	0	0	2	0	4	0	0	0	3	0	1
8	2	18	135.17	N	5	2	3	3	1	14	1	0	1	4	2	1

Day 5																
Stool Freq. during Day	SCCAI Day	Stool freq. during night	SCCAI Night	Total stool	CRP	Stools with Blood	SCCAI Amount of blood	SCCAI Urgency of defecation	SCCAI General Well Being	SCCAI EIMs	SCCAI	Abdominal Pain	Abdominal Tenderness	Need for anti diarrheal drugs	Stool Freq. during Day	SCCAI Day
6	1	3	1	9	9.42	3	2	3	3	0	10	1	0	0	3	0
2	0	0	0	2	3.92	0	0	0	0	0	0	0	0	0	1	0
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	0	0	0	3	20.2	0	0	0	1	0	1	0	0	0	2	0
2	0	0	0	2	11.74	1	1	0	2	0	3	0	0	0	1	0
6	1	6	2	12	10.78	10	2	2	4	0	11	1	0	1	6	1
5	1	4	2	9	45.2	6	2	2	4	0	11	1	0	0	6	1
3	0	0	0	3	1.9	0	0	1	2	0	3	0	0	0	2	0
6	1	3	1	9	26.58	4	2	2	3	0	9	1	0	0	3	0
5	1	1	1	6	60.73	0	0	2	3	0	7	1	0	0	2	0
6	1	2	1	8	47.62	3	2	1	3	0	8	1	0	0	3	0
5	1	5	2	10	46.8	7	2	2	3	0	10	1	0	1	5	1
2	0	0	0	2	5.06	0	0	0	1	0	1	0	0	0	1	0
3	0	0	0	3	4.98	0	0	0	2	0	2	0	0	0	3	0
4	1	1	1	5	104	4	2	2	2	0	8	0	0	0	2	0
3	0	0	0	3	90	0	0	1	2	0	3	0	0	0	2	0
6	1	3	1	9	6.04	4	2	1	4	0	9	1	0	0	5	1
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	1	4	2	10	34.52	8	2	3	4	0	12	1	0	1	10	3
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	1	4	2	10	21.44	7	3	3	4	0	13	1	0	1	4	1
6	1	3	1	9	37.3	3	2	3	3	0	10	1	0	0	4	1
1	0	0	0	1	1.02	0	0	1	1	0	2	0	0	0	1	0
7	2	5	2	12	0.09	12	3	2	3	0	12	1	0	1	2	0
1	0	1	1	2	5.94	1	1	1	1	0	4	0	0	0	2	0
6	1	4	2	10	69.6	8	2	2	4	0	11	1	0	1	4	1
5	1	4	2	9	18.72	4	2	2	3	0	10	1	0	0	4	1
2	0	0	0	2	2.22	0	0	0	1	0	1	0	0	0	2	0
5	1	4	2	9	1.23	4	2	2	3	0	10	1	0	0	5	1
2	0	0	0	2	1.28	0	0	0	1	0	1	0	0	0	2	0
3	0	1	1	4	10.8	0	0	0	0	0	1	0	0	0	3	0
3	0	0	0	3	12.5	0	0	0	0	0	0	0	0	0	4	0
Discharge	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18	3	6	2	24	3.06	0	0	3	4	0	12	1	0	1	9	2
4	1	0	0	4	21.5	0	0	0	0	0	1	0	0	0	2	0
2	0	8	2	10	7.33	5	2	3	3	0	10	1	0	1	6	1
Discharge	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Discharge	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	0	0	0	3	0.58	0	0	0	1	0	1	0	0	0	DISCHARGE	-
Discharge	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DISCHARGE	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DISCHARGE	-
5	1	2	1	7	28.72	2	2	3	3	0	10	1	0	0	5	1
Discharge	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	1	1	1	6	1.99	1	0	2	3	0	7	1	0	0	3	0
3	0	0	0	3	10.56	0	0	0	1	0	1	0	0	0	3	0
7	2	0	0	7	4.89	0	0	0	2	0	4	0	0	0	3	0
4	1	1	1	5	25.4	5	3	3	3	0	11	1	0	0	4	1
2	0	0	0	2	15.8	0	0	1	1	0	2	0	0	0	6	1
2	0	2	1	4	26.21	0	0	1	2	0	4	0	0	0	2	0
6	1	2	1	8	24.6	0	0	0	2	0	4	0	0	0	6	1
10	3	10	2	20	158.76	3	0	3	3	0	11	1	0	1	-	-

Day 7												Day					
Stool freq. during night	SCCAI Night	Total stool	CRP	Response at Day 7 Oxford Criteria	Stools with Blood	SCCAI Amount of blood	SCCAI Urgency of defecation	SCCAI General Well Being	SCCAI EIM	CRP	SCCAI	Stool Freq. during Day	SCCAI Day	Stool freq. during night	SCCAI Night	Total stool	Stools with Blood
1	1	4	2.64	N	1	1	3	4	0	2.64	9	-	-	-	-	-	-
0	0	1	24.7	y	0	0	0	0	0	24.7	0	4	2	0	0	4	0
-	-	-	-	N	-	-	-	-	-	-	-	-	-	-	-	-	-
0	0	2	4.54	Y	0	0	0	0	0	4.54	0	1	0	0	0	1	0
0	0	1	20.31	Y	0	0	1	2	0	20.31	3	3	0	1	1	4	0
4	2	10	45.6	N	7	2	2	3	0	45.6	10	-	-	-	-	-	-
3	1	9	41.19	N	6	2	3	4	0	41.19	11	-	-	-	-	-	-
1	1	3	0.38	Y	0	0	0	2	0	0.38	3	2	0	0	0	2	0
1	1	4	2.56	Y	1	1	1	2	0	2.56	5	3	0	0	0	3	0
1	1	3	6.49	Y	0	0	1	2	0	6.49	4	3	0	0	0	3	1
1	1	4	7.52	Y	1	1	1	2	0	7.52	5	2	0	0	0	2	0
3	1	8	60.23	N	8	2	2	4	0	60.23	10	-	-	-	-	-	-
0	0	1	12.4	Y	0	0	0	1	0	12.4	1	1	0	0	0	1	0
0	0	3	3.49	Y	0	0	0	1	0	3.49	1	3	0	0	0	3	0
1	1	3	13.5	Y	0	0	0	2	0	13.5	3	2	0	1	1	3	0
0	0	2	9.7	Y	0	0	0	1	0	9.7	1	2	0	0	0	2	0
1	0	6	49.5	N	2	2	1	3	0	49.5	7	2	0	1	1	3	0
-	-	-	-	N	-	-	-	-	-	-	-	-	-	-	-	-	-
4	2	14	98.7	N	10	2	3	4	0	98.7	14	-	-	-	-	-	-
-	-	-	-	N	-	-	-	-	-	-	-	-	-	-	-	-	-
2	1	6	45.5	N	4	2	2	4	0	45.5	10	-	-	-	-	-	-
3	1	7	7.71	N	5	2	3	3	0	7.71	10	-	-	-	-	-	-
0	0	1	0.98	Y	0	0	0	0	0	0.98	0	2	0	0	0	2	0
1	1	3	3.19	Y	1	1	1	2	0	3.19	5	2	0	0	0	2	0
0	0	2	4.15	Y	0	0	0	1	0	4.15	1	1	0	0	0	1	0
4	2	8	59.3	N	4	2	2	3	0	59.3	10	-	-	-	-	-	-
3	1	7	12.56	Y	3	2	1	4	0	12.56	9	6	2	3	1	9	4
0	0	2	2.43	Y	0	0	0	0	0	2.43	0	1	0	0	0	1	0
1	1	6	1.32	Y	2	2	1	2	0	1.32	7	5	2	3	1	8	4
0	0	2	0.39	Y	0	0	0	0	0	0.39	0	1	0	0	0	1	0
0	0	3	0.56	Y	0	0	0	1	0	0.56	1	LTFU	-	-	-	-	-
2	0	6	52.8	N	2	2	2	3	0	52.8	7	-	-	-	-	-	-
-	-	-	-	Y	-	-	-	-	-	-	-	1	0	0	0	1	0
4	2	13	1.89	N	1	1	3	3	0	1.89	11	-	-	-	-	-	-
0	0	2	10.58	Y	0	0	0	1	0	10.58	1	3	0	0	0	3	1
3	1	9	2.95	N	3	2	3	4	0	2.95	14	-	-	-	-	-	-
-	-	-	-	Y	-	-	-	-	-	-	-	LTFU	-	-	-	LTFU	-
-	-	-	-	Y	-	-	-	-	-	-	-	LTFU	-	-	-	LTFU	-
-	-	-	-	Y	-	-	-	-	-	-	-	2	0	0	0	2	0
-	-	-	-	Y	-	-	-	-	-	-	-	1	0	0	0	1	0
-	-	-	-	Y	-	-	-	-	-	-	-	2	0	0	0	2	0
3	1	8	56.47	N	5	2	2	2	0	56.47	8	-	-	-	-	-	-
-	-	-	-	Y	-	-	-	-	-	-	-	1	0	0	0	1	0
1	1	4	0.42	Y	0	0	1	2	0	0.42	4	6	2	3	1	9	5
0	0	3	24.7	Y	0	0	0	1	0	24.7	1	2	0	0	0	2	0
0	0	3	36.4	Y	0	0	0	2	0	36.4	2	1	0	0	0	1	0
3	1	7	58.4	N	4	3	2	4	0	58.4	11	-	-	-	-	-	-
3	1	9	2.5	N	2	2	2	3	0	2.5	9	2	0	0	0	2	0
0	0	2	12.4	Y	0	0	0	1	0	12.4	1	3	0	0	0	3	0
3	1	9	25.8	N	4	2	1	3	0	25.8	8	1	0	0	0	1	0
-	-	-	-	N	-	-	-	-	-	-	-	-	-	-	-	-	-

28					Week 8							Death		Rescue Therap	
SCCAI Amount of blood	SCCAI Urgency of defecation	SCCAI General Well Being	SCCAI EIMs	SCCAI	Stool Freq. during Day	Stool freq. during night	Total stool	Stools with Blood	SCCAI General Well Being	MAYO SCORE	CLINICAL REMISSION AS PER MAYO SCORE	Expired	Expired Day	Rescue Therapy	Which Rescue Therapy
-	-	-	-	-	Died	-	-	-	-	-	N	y	24	Y	COLECTOMY
0	0	1	0	3	3	0	3	0	1	2	Y	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	N	-	-	y	IFX
0	0	0	0	0	2	0	2	0	0	1	Y	-	-	-	-
0	1	1	0	3	3	0	3	0	1	2	Y	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	N	-	-	y	IFX
-	-	-	-	-	Died	-	-	-	-	-	N	y	13	Y	COLECTOMY
0	0	1	0	1	1	0	1	0	0	1	Y	-	-	-	-
0	0	2	0	2	2	0	2	0	2	2	N	-	-	-	-
1	2	2	0	5	2	1	3	0	1	2	Y	-	-	-	-
0	0	1	0	1	3	1	4	2	2	5	N	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	N	-	-	Y	COLECTOMY
0	0	0	0	0	2	0	2	0	0	1	Y	-	-	-	-
0	0	0	0	0	2	0	2	0	0	1	Y	-	-	-	-
0	0	1	0	2	3	0	3	0	1	2	Y	-	-	-	-
0	0	1	0	1	2	0	2	0	0	1	Y	-	-	-	-
0	0	1	0	2	2	0	2	0	1	2	Y	-	-	-	-
-	-	-	-	-	Died	-	-	-	-	-	N	y	3	-	-
-	-	-	-	-	Died	-	-	-	-	-	N	y	18	Y	COLECTOMY
-	-	-	-	-	-	-	-	-	-	-	N	-	-	Y	IFX
-	-	-	-	-	Died	-	-	-	-	-	N	y	32	y	IFX
-	-	-	-	-	Died	-	-	-	-	-	N	y	23	Y	COLECTOMY
0	0	0	0	0	1	0	1	0	0	1	Y	-	-	-	-
0	0	1	0	1	4	1	5	0	2	3	N	-	-	-	-
0	0	1	0	1	2	1	3	0	1	2	Y	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	N	-	-	Y	ifx
3	1	3	0	10	7	3	10	4	2	6	N	-	-	-	-
0	0	0	0	0	2	0	2	0	1	2	Y	-	-	-	-
3	1	3	0	10	5	4	9	3	2	6	N	-	-	-	-
0	0	0	0	0	1	0	1	0	0	1	Y	-	-	-	-
-	-	-	-	-	LTFU	-	-	-	-	-	N	-	-	y	IFX
-	-	-	-	-	-	-	-	-	-	-	N	-	-	y	IFX
0	0	0	0	0	1	-	1	0	0	1	Y	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	N	-	-	Y	ifx
1	0	1	0	2	2	0	2	2	2	6	N	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	N	-	-	Y	IFX
-	-	-	-	-	LTFU	-	-	-	-	-	N	-	-	-	-
-	-	-	-	-	LTFU	-	-	-	-	-	N	-	-	y	ifx
0	0	1	0	1	2	0	2	0	1	2	Y	-	-	-	-
0	0	0	0	0	1	-	1	0	0	1	Y	-	-	-	-
0	0	1	-	-	2	0	2	0	0	1	Y	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	N	-	-	y	IFX
0	0	0	0	0	1	-	1	0	0	1	Y	-	-	-	-
2	2	3	0	10	2	2	4	0	0	2	Y	-	-	-	-
0	0	1	0	1	3	0	3	0	1	2	Y	-	-	-	-
0	0	0	0	0	1	-	1	0	0	1	Y	-	-	y	ifx
-	-	-	-	-	-	-	-	-	-	-	N	-	-	Y	IFX
0	0	2	0	2	2	0	2	0	2	2	N	-	-	-	-
0	0	1	0	1	4	0	4	0	1	2	Y	-	-	-	-
0	0	0	0	0	3	1	4	0	2	3	N	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	N	-	-	Y	ifx

ıy	Adverse effects	Adverse effects														
Day on which Rescue Therapy Given	Facial edema	Hairfall	LVF	Hemoglobin	MCV	Neutrophils	Lymphocytes	NLR	Platelt Count	FBS	ESR	CRP	CRA	Fecal Calprotectin	Total cholestrol	LDL
6	-	-	-	8.2	81.4	21950	679	32.3269514	439	143	66	33.29	14.92825112	>2000	134	74
-	y	-	-	10.8	76.5	6002	1053	5.699905033	288	109	34	11.48	2.974093264	>2000	204	136
3	-	y	-	15.8	82.3	9630	920.2	10.46511628	304	102	12	18.61	3.934460888	>2000	146	92
-	y	-	-	7	61.9	11029	1726	6.389918888	677	97	65	126.58	46.53676471	1053	98	69
-	-	-	-	8.7	80.2	7429	1425	5.213333333	437	101	92	114.18	74.62745098	>2000	146	92
5	-	-	y	9.8	78.8	4386	906	4.841059603	342	67	18	51.15	28.41666667	>2000	57	22
7	-	-	-	11.2	81.3	7650	1744	4.38646789	338	-	67	92.36	47.85492228	>2000	142	98
-	y	-	-	9.7	80.8	5025	2692	1.866641902	438	-	-	1.33	0.318181818	>2000	99	47
-	-	-	-	11.9	81.4	5383	1337	4.02617801	343	106	56	115.98	38.78929766	434	125	67
-	y	-	-	7.4	113.7	3910	1537	2.543916721	73	91	70	326.5	127.0428016	-	-	-
-	-	-	-	10.8	76.2	8786	536	16.39179104	72	99	64	44.24	14.84563758	>2000	97	46
6	-	-	-	9.3	86.1	5234	1385	3.779061372	254	101	22	13.2	5.076923077	>2000	101	85
-	-	-	-	9.7	82.2	4841	4274	1.132662611	325	98	112	21.07	6.308383234	>2000	-	-
-	y	-	-	11.5	86.5	4724	1153	4.097137901	533	112	99	55.05	19.87364621	>2000	99	47
-	y	-	-	13.5	88.3	9797	3037	3.225880803	141	98	19	1.96	0.468899522	>2000	170	94
-	y	-	-	9.8	86.6	7167	1058	6.774102079	204	-	113	294.84	119.3684211	1947	112	68
-	-	-	-	12	75.1	12103	1690	7.161538462	332	105	14	29.69	7.119904077	>2000	142	88
-	-	-	-	12.2	80.4	20427	448	45.59598214	235	107	52	348.5	137.7470356	>2000	-	-
7	-	-	-	10.4	88.3	9897.2	741	13.35654521	239	101	2	28.25	24.56521739	>2000	85	40
6	-	-	-	8.4	72.6	6621.5	1663	3.981659651	322	94	19	64.07	19.35649547	>2000	88	48
5	-	-	-	10.3	79.7	27927	2055	13.58978102	247	102	18	327.25	193.6390533	>2000	98	56
7	-	-	-	8.6	71.2	9222	848	10.875	254	110	-	73.42	44.76829268	>2000	39	21
-	y	-	-	8.3	93.6	1722	1714	1.004667445	371	109	87	8.59	5.143712575	>2000	85	40
-	y	-	-	13.7	86.8	2169	1688	1.284952607	96	106	26	0.8	0.218579235	1987	157	70
-	-	-	-	6.5	62.3	14331	1260	11.37380952	771	101	29	65.39	24.76893939	>2000	141	79
7	-	-	-	10.9	90.3	21561	247	87.29149798	94	103	79	99.8	54.53551913	>2000	139	82
-	-	-	-	9.2	89.6	4176	830	5.031325301	590	100	71	99.73	44.52232143	>2000	130	75
-	y	-	-	11.7	73.2	4742	1931	2.455722424	251	119	23	48.32	13.45961003	1908	137	84
-	y	-	-	9.9	67.1	3864	1575	2.453333333	140	109	7	0.56	0.176100629	>2000	134	78
-	y	-	-	13.6	83.1	8151	1455	5.602061856	398	106	32	7.83	1.947761194	1088	128	67
29	-	-	-	9.7	76.1	8770	6100	1.437704918	251	-	52	111.83	41.88389513	-	-	-
7	-	-	-	10.2	80.2	8110	1360	5.963235294	338	-	39	30.5	8.155080214	>2000	-	-
-	y	-	-	4.2	-	4140	4290	0.965034965	284	-	-	0.17	0.045698925	210	-	-
7	-	-	-	12.1	79.6	6310	23.3	270.8154506	351	136	28	41.96	11.49589041	-	-	-
-	y	-	-	7.6	78	2849	322	8.847826087	298	-	-	2.54	0.811501597	>2000	-	-
7	-	-	-	9.6	71.4	5830	24.8	235.0806452	311	-	52	25.1	7.191977077	-	-	-
-	y	-	-	9.3	86.5	8915	2507	3.556043079	154	-	2	129.29	97.21052632	-	-	-
56	-	-	-	11.9	80.3	10738	1202	8.93344426	185	-	14	0.85	0.194063927	44	-	-
-	-	-	-	9.9	76.5	6440	1245	5.172690763	240	-	-	10.59	3.589830508	-	-	-
-	-	-	-	14.6	-	5644	1290	4.375193798	261	-	47	9.72	2.43	>2000	-	-
-	-	-	-	7.2	67.6	3120	5570	0.560143627	467	-	-	1.61	0.461318052	-	-	-
6	-	-	-	9.7	78.1	9450	3600	2.625	457	70	50	76.28	29.22605364	106	-	-
-	-	-	-	11.6	73.7	9126	2419	3.77263332	360	-	39	54.08	12.63551402	-	-	-
-	-	-	-	9.5	63.4	3210	6430	0.499222395	241	112	14	22.81	6.768545994	-	-	-
-	-	-	-	11	76.9	7200	1700	4.235294118	387	-	18	30.55	8.018372703	>2000	-	-
60	-	-	-	11.5	89.8	7866	2052	3.833333333	370	-	22	14.89	4.35380117	565	-	-
7	-	-	-	10.5	75.3	6240	2520	2.476190476	600	105	6	93.68	31.7559322	>2000	-	-
-	-	-	-	12.3	69.4	6200	1400	4.428571429	289	98	22	31.32	6.96	>2000	119	74
-	-	-	-	13.5	101.1	5240	3450	1.51884058	258	81	11	41.27	10.42171717	1008	-	-
-	-	-	-	7.5	29.2	2020	172	11.74418605	88	-	-	18.36	7.256916996	929	-	-
6	-	-	-	10.9	76.8	640	1720	0.372093023	320	78	63	135.17	36.73097826	>2000	-	-

Investigations Day 0																				
HDL	Triglyceride	Total Bilirubin	Direct Bilirubin	ALT	AST	ALP	Total Protein	Albumin	Urea	Creatinine	HBsAg	Anti-HCV	CMV(inclusion bodies)	CMV(IHC)	EBER	Mantoux	GDH	Toxin A	Toxin B	Chest X ray
44	114	0.32	0.04	8	8	56	4.8	2.23	37	1.08	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
54	66	0.24	0.12	14	16	78	7.2	3.86	15	0.56	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
46	53	0.52	0.15	38	22	141	7.3	4.73	30	0.99	NEG	NEG	NEG	NEG	3	NEG	NEG	NEG	NEG	WNL
21	109	0.78	0.29	9	20	185	6.8	2.72	33	1.71	NEG	NEG	NEG	NEG	4	NEG	NEG	NEG	NEG	WNL
46	53	0.21	0.11	4	14	73	4.2	1.53	30	0.33	NEG	NEG	NEG	NEG	38	NEG	NEG	NEG	NEG	WNL
16	69	0.34	0.16	10	13	182	3.4	1.8	7	0.28	NEG	NEG	NEG	POSITIVE	-	NEG	NEG	NEG	NEG	WNL
41	120	0.49	0.14	44	14	94	4.7	1.93	40	0.96	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
42	45	0.49	0.08	120	64	85	7.7	4.18	23	0.47	NEG	NEG	NEG	-	-	NEG	POS	POS	POS	WNL
26	105	0.55	0.31	24	25	99	5.2	2.99	40	0.87	NEG	NEG	NEG	-	-	NEG	NEG	NEG	POS	WNL
-	-	1	0.74	17	29	66	4.9	2.57	72	0.97	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
40	88	0.27	0.19	9	22	65	5.3	2.98	12	0.64	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
43	119	0.1	0.03	16	19	120	5.2	2.6	13	0.23	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
-	-	0.21	0.09	9	15	91	6.5	3.34	14	0.98	NEG	NEG	NEG	-	-	NEG	NEG	NEG	WNL	WNL
42	45	0.29	0.02	9	11	70	6.3	2.77	11	0.58	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
69	69	0.49	0.08	120	64	85	7.7	4.18	37	0.77	NEG	NEG	NEG	NEG	1	NEG	NEG	NEG	WNL	WNL
42	105	0.21	0.08	59	12	123	5.3	2.47	11	0.83	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	WNL	118
25	112	0.26	0.1	11	16	72	6.7	4.17	12	0.84	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
-	-	0.53	0.21	16	28	122	5.3	2.53	30	0.98	-	-	-	-	-	-	-	-	-	BILATERAL INFILTRATES
35	96	0.34	0.25	84	30	640	3	1.15	8	0.13	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
35	112	0.52	0.22	11	16	77	6.4	3.31	31	0.77	NEG	NEG	-	NEG	-	NEG	NEG	NEG	NEG	WNL
19	97	0.38	0.12	9	14	45	4	1.69	9	0.28	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
15	59	0.35	0.2	14	20	172	4.4	1.64	17	0.35	NEG	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	WNL
39	76	0.13	0.06	8	15	126	6	1.67	11	0.62	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
40	375	0.35	0.14	19	17	93	6.5	3.66	33	0.78	NEG	NEG	NEG	POSITIVE	4	NEG	NEG	NEG	NEG	WNL
51	145	0.49	0.13	9	14	85	5.7	2.64	18	0.84	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
42	151	0.96	0.23	10	20	150	4.1	1.83	14	0.48	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
42	150	0.38	0.09	18	20	73	5.5	2.24	21	0.68	NEG	NEG	NEG	POSITIVE	4	NEG	NEG	NEG	NEG	WNL
34	166	0.3	0.16	23	20	88	6.5	3.59	22	0.83	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
41	152	0.42	0.12	19	19	127	5.9	3.18	16	0.67	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
48	94	0.71	0.15	18	17	81	7.7	4.02	19	0.69	NEG	NEG	NEG	-	-	NEG	NEG	NEG	NEG	WNL
-	-	-	-	-	-	-	-	2.67	-	2.46	Neg	Neg	NEg	neg	neg	neg	neg	neg	neg	-
-	-	-	-	-	-	-	-	3.74	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	3.72	-	-	-	-	-	-	-	-	-	-	-	-
-	-	0.32	0.13	15	17	79	6.4	3.65	15	0.59	NEG	NEG	NEG	-	-	NEG	POSITIVE	POSITIVE	POSITIVE	-
-	-	-	-	-	-	-	-	3.13	-	0.78	-	-	-	-	-	-	-	-	-	-
-	-	0.31	0.06	19	11	51	6.9	3.49	12	1.04	-	-	NEG	-	-	-	NEG	NEG	NEG	-
-	-	-	-	-	-	-	-	1.33	-	1.25	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	4.38	-	0.47	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	2.95	-	0.6	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	4	-	0.67	-	-	-	-	-	-	-	-	-	-
-	-	0.15	0.07	9	8	61	7.4	3.49	15	0.58	-	-	-	NEG	4	-	-	-	-	-
-	-	0.48	0.11	12	15	46	5.3	2.61	19	0.41	NEG	NEG	NEG	NEG	3	-	NEG	POSITIVE	POSITIVE	-
-	-	-	-	-	-	-	-	4.28	-	-	-	-	-	-	-	-	-	-	-	-
-	-	0.54	0.09	101	91	63	6.1	3.37	19	0.77	NEG	NEG	-	-	-	NEG	NEG	NEG	NEG	-
-	-	-	-	-	-	-	-	3.81	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	3.42	-	0.87	-	-	-	-	-	-	-	-	-	-
-	-	-	-	16	16	58	-	2.95	27	0.75	NEG	NEG	NEG	-	-	NEG	-	NEG	NEG	NORMAL
40	54	-	-	23	10	81	-	4.5	18	0.75	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NORMAL
-	-	0.62	0.02	6	20	69	6.4	3.96	12	70	-	-	NEG	NEG	NEG	-	POSITIVE	NEG	POSITIVE	-
-	-	-	-	-	-	-	-	2.53	-	0.54	-	-	-	-	-	-	-	-	-	-
-	-	1.02	0.48	36	24	103	7.3	3.68	26	0.7	NEG	NEG	-	-	-	-	POSITIVE	POSITIVE	POSITIVE	-

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The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.10.2021 has approved the plan of thesis of **Manjeet Kumar Goyal**, a student of your college for **DM Medical Gastroenterology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

A prospective placebo controlled randomized clinical study of tofacitinib as an adjunct to corticosteroids in acute severe ulcerative collitis.

Supervisor
Dr. Varun Mehta
Prof.,
Dept. of Gastroenterology,
DMCH, Ludhiana.

Co-Supervisor

Dr. Ajit Sood
Prof. & Head,
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Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

165. If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.

166. The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.

A PROSPECTIVE PLACEBO CONTROLLED RANDOMIZED CLINICAL STUDY OF TOFACITINIB AS AN ADJUNCT TO CORTICOSTEROIDS IN ACUTE SEVERE ULCERATIVE COLLITIS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

IN

GASTROENTEROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

AUGUST, 2021

DR. MANJEET KUMAR GOYAL

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ABSTRACT OF PLAN OF THESIS

Title	**A PROSPECTIVE PLACEBO CONTROLLED RANDOMIZED CLINICAL STUDY OF TOFACITINIB AS AN ADJUNCT TO CORTICOSTEROIDS IN ACUTE SEVERE ULCERATIVE COLLITIS**
For the degree of	D.M. (Gastroenterology)
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Introduction: Ulcerative Colitis (UC), a type of inflammatory bowel disease (IBD) is characterized by contiguous superficial mucosal inflammation of the colon that extends proximally, and may lead to ulcerations, severe bleeding, etc. Although, over the years, targeted therapies including biologicals have been tried for the management of UC but these agents have their own limitations. This study intends to evaluate the efficacy of tofacitinib as an adjunct to corticosteroids versus corticosteroids alone in the management of patients with acute severe UC.

AIM: To evaluate the effectiveness of tofacitinib as adjunctive therapy to intravenous hydrocortisone in patients with acute severe ulcerative collitis.

MATERIAL AND METHOD: Placebo controlled randomized clinical study in patients with ASUC which will be conducted on patients attending the outpatient department or admitted in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India.

CLINICAL SIGNIFICANCE: To evaluate efficacy of tofacitinib as an adjuncts to steroids in the management of ASUC.

Keywords: UC: Ulcerative Colitis, ASUC: Acute Severe Ulcerative Collitis

Manjeet Kumar Goyal
Candidate's Sign

Co-supervisor's Sign

Supervisor's Sign

Principal's Sign

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"A PROSPECTIVE PLACEBO CONTROLLED RANDOMIZED CLINICAL STUDY OF TOFACITINIB AS AN ADJUNCT TO CORTICOSTEROIDS IN ACUTE SEVERE ULCERATIVE COLLITIS"** exist in the Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself/herself under our supervision and guidance.

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4	DATE OF ADMISSION OF COURSE	24TH DECEMBER, 2020
5	TITLE OF THE TOPIC	A PROSPECTIVE PLACEBO CONTROLLED RANDOMIZED CLINICAL STUDY OF TOFACITINIB AS AN ADJUNCT TO CORTICOSTEROIDS IN ACUTE SEVERE ULCERATIVE COLLITIS

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Ulcerative Collitis (UC) is a chronic immune-mediated inflammatory condition of the large intestine that is frequently associated with inflammation of the rectum but often extends proximally to involve additional areas of the colon. The absence of rectal involvement has been noted in fewer than 5% of adult patients with UC at diagnosis but may be seen in up to one-third of pediatric-onset colitis.[1] The initial presentation of new UC is characterized by symptoms of an inflamed rectum, namely, bleeding, urgency, and tenesmus (a sense of pressure). The condition may present at any time and at all ages, but there is a predominant age distribution of onset that peaks between ages 15 and 30 years. The pattern of disease activity is most often described as relapsing and remitting, with symptoms of active disease alternating with periods of clinical quiescence, which is called remission. Some patients with UC have persistent disease activity despite diagnosis and medical therapy, and a small number of patients present with the rapid-onset progressive type of colitis known as fulminant disease.[2,3]

Determination of the extent and severity of disease is important to select the appropriate treatment algorithm. Extent of the disease should be characterized according to the Montreal classification as proctitis (E1), left-sided colitis (E2), or extensive colitis (E3) (extension proximal to the splenic flexure).[4,5] Commonly, severity of UC has been classified according to the Truelove and Witts' [6] criteria published in 1955. Mild colitis is defined as fewer than 4 bowel movements daily, normal temperature, heart rate, hemoglobin (>11 g/dL), and ESR (<20 mm/hr). Severe disease is defined by bowel frequency greater than 6 times a day in conjunction with fever, tachycardia, anemia, or an elevation in ESR. The treatment goals of ulcerative colitis (UC), include induction and maintenance of remission; improvement in quality of life of patients with least adverse effects and complications and at an affordable cost to the patients. Although, over years, targeted therapies

including biologics have been added to the armamentarium of conventional medical therapies of UC, these agents have their own limitations. Clinical trials and real-world evidence show that biologics are costly, are associated with adverse effects like high incidence of infectious diseases, and importantly, have high rates of primary and secondary non-response, thus forcing the researchers to look for alternatives and new treatment options.

Tofacitinib, a JAK-STAT (Janus kinase-signal transducers and activators of transcription) inhibitor and an anti-inflammatory drug, is a new addition to the treatment modalities for UC. Janus kinases are intracellular tyrosine kinases which mediate the signal transduction of various cytokines involved in the inflammatory reactions in IBD, like IL-6, IL-7, Il-10, IL-12, IFNα, IFNβ 2, 4, 7, 9 etc. The advantages of JAK-STAT inhibitors over monoclonal antibodies include, the oral administration, predictable pharmacokinetics with reduced plasma half-life, rapid onset of action, quick clearance, lack of immunogenicity and an intracellular target. Additionally, tofacitinib has a broader spectrum whereas biologics are generally selective for a cytokine or integrin. Therefore, this study is planned to evaluate the efficacy of tofacitinib as an adjunct to corticosteroid in the management of acute severe ulcerative colitis and compare it with corticosteroids alone.

6.2 REVIEW OF LITERATURE

UC is a chronic inflammatory bowel disease with peak onset in early adulthood.[3] Untreated, the natural history of the disease is one of relapsing and remitting mucosal inflammation. Based on population-based cohort studies, the majority of patients with UC have a mild to moderate course, generally most active at diagnosis and then in varying periods of remission or mild activity. Approximately 15% patients may experience an aggressive course, and 20% of these patients may require hospitalization for severe disease activity.[3,7] The 5- and 10-year cumulative risk of colectomy is 10%–15%, primarily limited to patients with moderate to severe disease activity; a subset of hospitalized patients with acute severe ulcerative colitis (ASUC) have short-term colectomy rates of 25%–30%.[7] Predictors of an aggressive disease course and colectomy are the following: young age at diagnosis (<40 years old), extensive disease, severe endoscopic activity (presence of large and/or deep ulcers), presence of extra-intestinal manifestations, early need for corticosteroids, and elevated inflammatory markers.[8]

Acute Severe Ulcerative Collitis (ASUC) is a medical emergency and a potentially life-threatening condition that requires prompt recognition and early initiation of treatment. Acute severe ulcerative colitis (ASUC) is defined as the presence of 6 or more bowel movements daily accompanied by at least 1 systemic sign of toxicity including tachycardia, fever, anemia (hemoglobin, 10.5 g/dL), or elevated inflammatory markers (ESR 30 mm/hr).[6]

Infectious causes of colitis should be ruled out by stool microscopy and bacterial culture, ELISA or PCR, in particular C.difficile infection. Pseudomembranous colitis is a potential manifestation of C. difficile infection that confers an additional risk of colectomy and mortality.[9] Various tests are available for the diagnosis of CDI in ASUC, the most common ones being ELISA against C. diff toxins A + B and nucleic acid amplification tests such as PCR.[10] The latter tests are more sensitive, but emerging evidence suggests that they may result in false-positive

results, particularly in patients without documented diarrhea.[10] In 1 series, up to 47% of hospitalizations for UC were associated with CDI.[11] Although other cohorts have reported a lower frequency, patients with UC and CDI have a 4-fold increase in mortality, longer hospital stays, and higher rate of colectomy, emergency department visits, therapy escalation, and hospitalizations up to 1 year after the index episode.[11-14] Although controlled trial data are limited, emerging evidence suggests a higher failure rate with metronidazole, suggesting that oral vancomycin should be the first-line agent for treatment of CDI in the hospitalized patient with ASUC.[10,15]

Tofacitinib has been used in the management of rheumatoid arthritis for the last many years; however, it has been studied and approved for moderate-severe ulcerative colitis (UC) cases in the last couple of years only. The phase 3 clinical trials for induction therapy, OCTAVE induction (1 and 2) have demonstrated significantly higher rates of remission, mucosal healing and improvement in health-related quality of life in tofacitinib treatment arms as compared to placebo.[16] The maintenance treatment study, OCTAVE Sustain, also showed that the treatment end-points were maintained at 52 weeks with tofacitinib as compared to placebo.[16] US FDA and EMA approved tofacitinib for treatment of adult patients with moderately to severely active UC.[17] Post hoc analysis of phase III clinical studies have shown that efficacy and safety of tofacitinib among East Asian population (Japan, Korea, Taiwan) is comparable to the global analysis.[18] In a real-world cohort, clinical remission was achieved among 33% patients of moderately severe active UC patients who had failed treatment with two classes of biologic therapies. However, there was no dose-response relationship with 5 mg and 10 mg doses of tofacitinib. After one year, 42% of patients remained in steroid-free clinical remission.[19,20]

Increased incidence rates of infections, including herpes zoster, have been reported from patients with rheumatoid arthritis and psoriasis. In the OCTAVE (1 and 2) and OCTAVE Sustain, similar proportions of patients across treatment groups had adverse events. However, herpes zoster infections were significantly higher in tofacitinib (10 mg

BD) group as compared to placebo.[21] The most common adverse events in both treatment arms of OCTAVE sustain trial were nasopharyngitis, arthralgia and headache. Results of the open label long term extension study from the OCTAVE Sustain, show a higher proportion of patients with abnormal creatine kinase and lipid levels in the tofacitinib groups as compared to placebo.[22] US FDA has recently issued preliminary results from a safety clinical trial about the increased risk of serious heart-related problems and cancer with tofacitinib (both immediate release and extended release preparations) as compared to TNF-α antagonists.[16]

The efficacy of tofacitinib has been demonstrated in the treatment of moderate to severe ulcerative colitis (UC). However, there is limited data on use of tofacitinib in the setting of acute severe ulcerative colitis (ASUC). Bernstein et al recently published a case series of four patients with ASUC treated with tofacitinib where three out of four patients were able to achieve clinical remission and 50% were able to avoid colectomy.[23] Intravenous corticosteroids are the mainstay of therapy for acute severe ulcerative colitis (ASUC), but 30%-40% of patients fail to respond. This randomized placebo controlled trial aims to evaluate the efficacy of tofacitinib used as an adjunct to corticosteroids versus corticosteroids alone in patients with ASUC.

6.3 AIMS AND OBJECTIVES OF THE STUDY

- To evaluate the effectiveness of tofacitinib as adjunctive therapy to intravenous hydrocortisone in patients with ASUC.

7. MATERIALS AND METHODS

STUDY DESIGN

This is a placebo controlled randomized clinical study in subjects with ASUC.

This study will be conducted on the patients attending the outpatient department or admitted in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India.

Patients with acute severe UC (defined as 6 or more stools with blood and 1 or more of the following hemoglobin <10.5 g/dL, erythrocyte sedimentation rate [ESR] >30 mm/hr or CRP > 30 mg/L, fever >37.8°C, or tachycardia >90/min; the modified Truelove Witts criteria) and fulfilling all other inclusion/exclusion criteria will be randomized. A computer-generated randomization schedule will be used to assign subjects to either of the two groups at a 1:1 allocation ratio.

Group 1: Intravenous hydrocortisone (300 mg per day in three divided doses) plus Tofacitinib (10 mg thrice daily) for 7 days

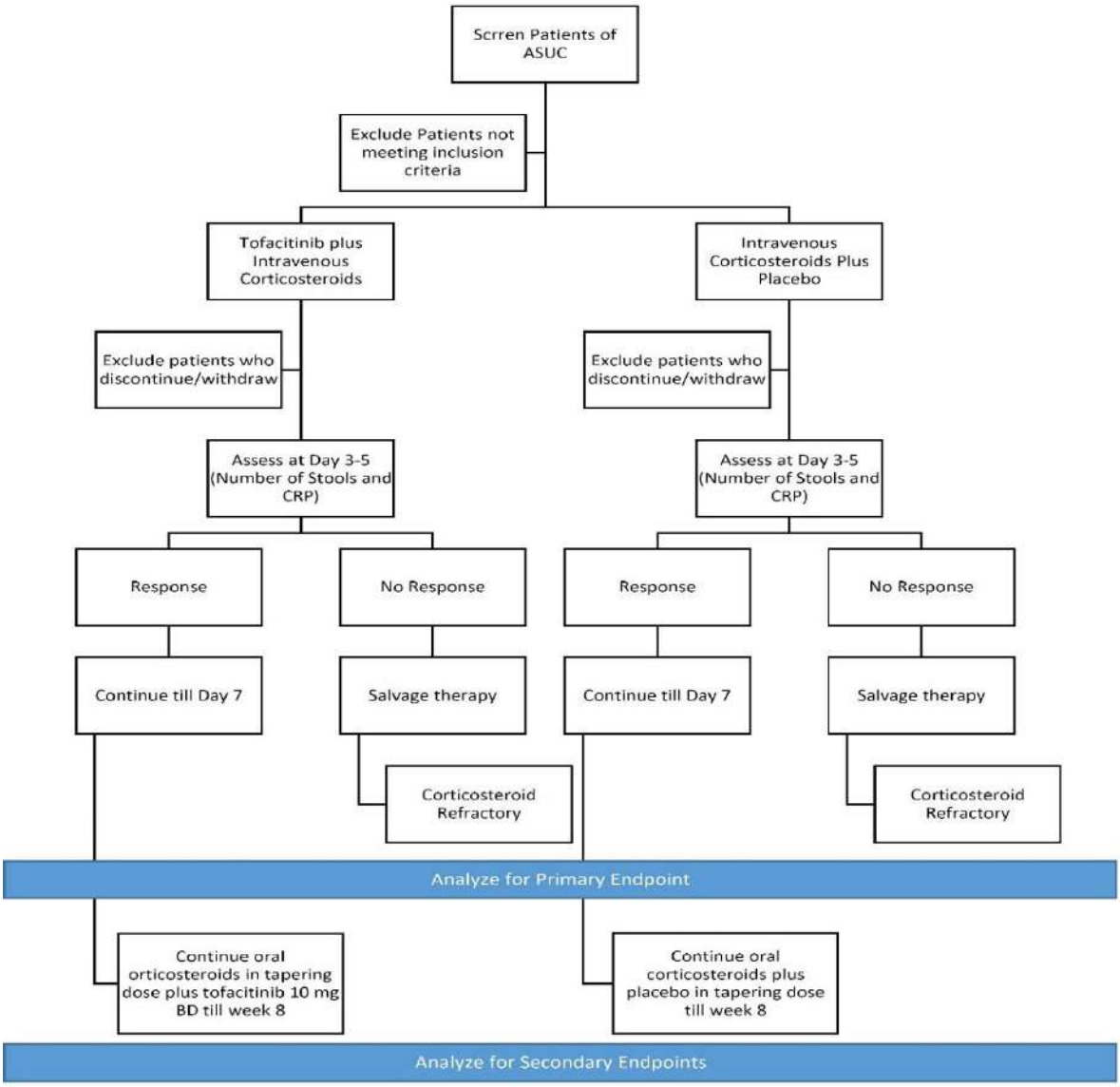
Group 2: Intravenous hydrocortisone (300 mg per day in three divided doses) plus Placebo (thrice daily) for 7 days.

All the enrolled patients will continue to receive other standard of care drugs (including prophylaxis for deep venous thrombosis) irrespective of the allocation of treatment groups.

Subjects will be assigned a subject number in the order of their acceptance into the study. This identifying number will be retained throughout the study.

Rescue treatment

Patients who fail to respond to treatment (defined as patients with >8 stools/day, or 3–8 stools/day with CRP >45 mg/L between days 3 and 5), necessitating initiation of salvage medical therapy (biologics/cyclosporine) or colectomy would be started on appropriate treatment at the discretion of the investigator.


Scrren Patients of ASUC
Exclude Patients not meeting inclusion criteria
Tofacitinib plus Intravenous Corticosteroids
Intravenous Corticosteroids Plus Placebo
Exclude patients who discontinue/withdraw
Exclude patients who discontinue/withdraw
Assess at Day 3-5 (Number of Stools and CRP)
Assess at Day 3-5 (Number of Stools and CRP)
Response
No Response
Response
No Response
Continue till Day 7
Salvage therapy
Continue till Day 7
Salvage therapy
Corticosteroid Refractory
Corticosteroid Refractory
Analyze for Primary Endpoint
Continue oral orticosteroids in tapering dose plus tofacitinib 10 mg BD till week 8
Continue oral corticosteroids plus placebo in tapering dose till week 8
Analyze for Secondary Endpoints

Informed Consent

The protocol, informed consent form(s), recruitment materials and all participant materials will be submitted for IEC review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require IEC review and approval before the changes are implemented in the study. The process of informed consent will be initiated prior to the individual agreeing to participate in the study and will continue throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IEC-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study.

7.1 SOURCES OF DATA

Patients diagnose with acute severe ulcerative colitis as per modified Truelov and Witt's criteria admitted indoors in Department of Gastroenterology, DMC & H will be enrolled for the study.

7.2 METHODS OF COLLECTION OF DATA

Confirmed cases of IBD will be enrolled and the appropriate investigations will be done. Daily stool frequency and questionnaire will be filled. Patients will be followed-up every day for first 7 days followed by on day 14 and after 8 weeks from the day of enrollment.

INCLUSION CRITERIA

1. Patients with acute severe ulcerative colitis (defined by Truelove Witts Criteria)
2. Subject must be at least 18 years of age.
3. Subjects who are willing and able to comply with treatment plan, laboratory tests, daily bowel movement diary call, and other study procedures.
4. Subjects who are willing to provide a written informed consent.

EXCLUSION CRITERIA

1. Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn's Disease.
2. Subjects displaying clinical signs of fulminant colitis or toxic megacolon
3. Subjects infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses
4. Subjects who have been vaccinated with live or attenuated vaccine within 6 weeks of baseline or scheduled to receive these vaccines during study period or within 6 weeks after last dose of study medication
5. Subjects with malignancies or a history of malignancies, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin.

6. Subjects with current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological disease.
7. Pregnant females

SCALES AND SCORES

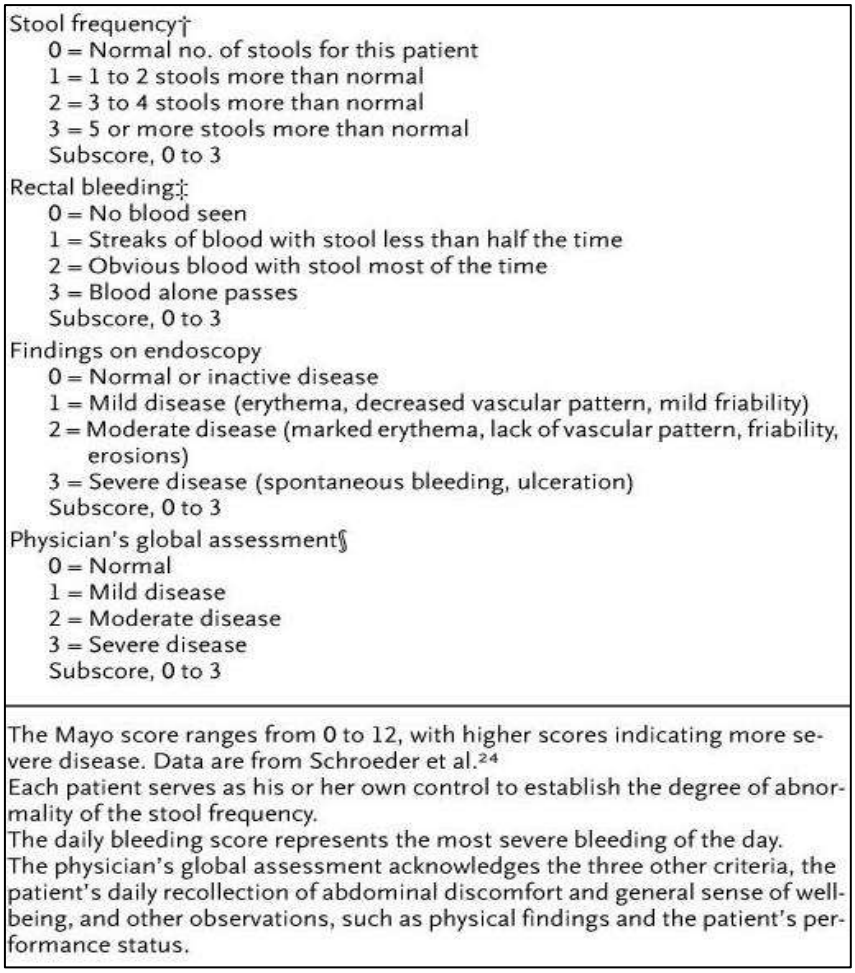
Disease Classification

- The Montreal Classification will be used to classify UC.

Montreal Classification for adult UC		
Term	Distribution	Description
E1	Proctitis	Involvement limited to the rectum (i.e. proximal extent of inflammation is distal to the recto-sigmoid junction)
E2	Left sided colitis	Left-sided involvement limited to the proportion of the colon distal to the splenic flexure (analogous to 'distal' colitis)
E3	Extensive colitis	Extensive involvement extends proximal to the splenic flexure, including pancolitis

Disease severity

- Disease severity will be defined by the Mayo score.



Stool frequency†
0 = Normal no. of stools for this patient
1 = 1 to 2 stools more than normal
2 = 3 to 4 stools more than normal
3 = 5 or more stools more than normal
Subscore, 0 to 3

Rectal bleeding‡
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passes
Subscore, 0 to 3

Findings on endoscopy
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Subscore, 0 to 3

Physician's global assessment§
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Subscore, 0 to 3

The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Data are from Schroeder et al.[24]
Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
The daily bleeding score represents the most severe bleeding of the day.
The physician's global assessment acknowledges the three other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Fig.1. Mayo Clinic Score

Acute Severe UC will be defined on the basis of modified Truelove Witts Criteria.

Parameter	Mild	Moderate	Severe
Bloody stool/day	<4	≥4 or more if	≥6 and
Pulse	<90 bpm	≤90 bpm	> 90 bpm or
Temperature	<37.5 C	≤ 37.8 C	> 37.8 C or
Haemoglobin	>11.5 g/dL	>10.5 g/dL	<10.5 g/dL
ESR or	<20 mm/h	≤ 30 mm/h	>30 mm/h or
CRP	normal	≤ 30 mg/l	>30 mg/l

Fig.2. Modified Truelove Witts Criteria

Symptom	Score
Bowel frequency (per day)	
1-3	0
4-6	1
7-9	2
>9	3
Bowel frequency (per night)	
0	0
1-3	1
4-6	2
Urgency of defecation	
None	0
Hurry	1
Immediately	2
Incontinence	3
Blood in stool	
None	0
Trace	1
Occasionally frank	2
Usually frank	3
General well-being	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
Extracolonic manifestations	
(Uveitis, pyoderma gangrenosum, erythema nodusum, arthropathy)	1 per manifestation

Fig.4 The Simple Clinical Colitis Activity Index (SCCAI)

Definition of response to corticosteroids ± tofacitinib (Primary end point)

- Remission: Defined as ≤3 stools/day with the absence of visible blood at day 7.
- Refractory: Patients with >8 stools/day, or 3–8 stools/day with CRP >45 mg/L between days 3 and 5

Definitions of Secondary end points based on Mayo Clinic Score

- Clinical remission will be defined by a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding sub-score of 0.
- Clinical response will be defined by a decrease from baseline in Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1.
- Endoscopic remission will be defined by Mayo endoscopic subscore of 0.
- Mucosal healing will be defined by Mayo endoscopic subscore of 0 or 1

DURATION OF STUDY

The study duration will be one year (1st April 2021- 31st March 2022) with enrolment period of ten months (1st April 2021- 31st January 2022) and a follow up period of 8 weeks for each enrolled subject.

OUTCOME

1. Endpoints

Primary Endpoint

- To compare the rates of corticosteroid responsiveness in the two groups at Day 7.

Secondary endpoints

- To compare the difference in inflammatory biomarkers (C-reactive protein and fecal calprotectin) in the two groups at week 8.

- To compare the proportion of patients in clinical remission at week 8.
- To compare the proportion of patients in endoscopic remission at week 8, if possible.

STATISTICAL ANALYSIS

The primary endpoint will be the proportion of patients responsive to corticosteroids in both the groups. For each comparison, the significance level will be set at 0.05. All statistical analyses will be performed using Stata 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

- Yes, the study requires investigations

The following investigations will be carried out in all the enrolled subjects.

1. Hemogram.
    i. Hemoglobin.
    ii. TLC
    iii. Platelet count.
2. Erythrocyte Sedimentation Rate
3. C-Reactive Protein (quantitative)
4. Fecal Calprotectin (Quanton Cal Kit)
5. Liver Function Tests.
    i. AST (Aspartate aminotransferase).
    ii. ALT (Alanine aminotransferase).
    iii. ALP (Alkaline phosphatase).
    iv. Bilirubin.
    v. Total protein.
    vi. Albumin.

6. Renal Function Tests
    i. Blood Urea.
    ii. Serum Creatinine.
7. Fasting Blood Sugar.
8. Lipid profile
    i. Cholesterol (Total, HDL, LDL, VLDL)
    ii. Triglycerides
9. Hepatitis B surface antigen (HBs Ag)
10. Anti-Hepatitis C antibodies (Anti HCV)
11. Sigmoidoscopy (unprepared)
12. Stool for Clostridioides difficile toxin
13. Rectal biopsy for CMV (histopathology and immunohistochemistry)

Monitoring for adverse effects (AE)

Safety will be assessed by physical examinations, clinical and laboratory results and the spontaneous reporting of AEs, in all subjects. AEs experienced by participants involved in the study will be reported to the site's IEC in accordance with their procedures. Subjects will be monitored for development of any infection (viral, bacterial, and fungal). A subject who experiences a serious infection (defined as any infection requiring parenteral antibiotics or hospitalization) would be discontinued from the study. A serious infection would be reported as a serious adverse event (SAE). Subjects who experience non-serious infections that require treatment may be continued on the drug but a record would be mentioned in the CRF. All enrolled subjects would be followed closely for identification of a cardiovascular/ venous thromboembolism event.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith.

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PROFORMA

CRF : Tofacitinib as an adjunct to Corticosteroids in ASUC

Drug Code

Patient ID | Date of Enrolment | Group : 1 / 2

Date of Birth | Age | Sex

Year of Onset of Symptoms | Year of Diagnosis

Age at Diagnosis

Addictions: Smoking / Alcohol / Opium / IVDU / Others (Please specify)/Nil

Comorbidity HTN/ T2DM/ Bronchial Asthma / CAD/ COAD/ Thyroid disorder/ CVA/ Others/Nil

Family history of IBD: Yes/No (If Yes, specify)

Appendicectomy: Yes/No

Disease Characteristics at Enrolment

Ulcerative Colitis		**Crohn's Disease**	
Colonoscopic Extent		Classification	A L B P
		CDAI	
Partial Mayo Score		CTE/MRE/ DBE/ Colonoscopy/UGIE (if Required)	
Total Mayo Clinic Score		Capsule Endoscopy (If Required)	
Histopathology	**Supportive/ Consistent**	Histopathology	**Supportive/ Consistent**

Personal and Past History

Previous Medications	
ATT	
Alternative Medicine	
Others (if any)	
Past History	
Tuberculosis	
Chicken pox/shingles	
Jaundice	
Surgery	
Comorbidities	
Liver Disease/DM/HTN/Others	
Family History	
IBD/Liver Disease/Tuberculosis/Others	

Signature of Candidate **Signature of Supervisor** i

Number of previous hospital admissions due to ASUC

Details of visit(s):

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Week 2	Week 4	Week 8
Vitals and Anthropometry											
Blood Pressure											
Temperature											
Heart Rate											
Weight											
Height		X	X	X	X	X	X	X	X	X	
BMI		X	X	X	X	X	X	X	X	X	
Disease Characteristics											
Number of Stools											
Number of Stools with Blood											
Total Mayo Clinic Score		X	X	X	X	X	X	X	X	X	
Partial Mayo Clinic Score											
SCCAI											
Endoscopic Mayo Clinic Score		X	X	X	X	X	X	X	X	X	

Medications (Please ☑ if applicable and specify the dose)											
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Week 2	Week 4	Week 8
5-ASA Oral											
5-ASA Rectal											
Tofacitinib											
Corticosteroids IV											
Corticosteroids Oral											
Corticosteroids Rectal											
Azathioprine											
6-MP											
Others (Please specify the name and dose)											
Rescue Therapy if refractory /complications (Please specify the name and dose)											

Signature of Candidate **Signature of Supervisor**

Investigations											
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Week 2	Week 4	Week 8
Hemoglobin		X	X	X	X	X	X	X	X	X	
Total Leucocyte Count		X	X	X	X	X	X	X	X	X	
Platelets		X	X	X	X	X	X	X	X	X	
ESR		X	X	X	X	X	X	X	X	X	
CRP quantitative		X	X	X	X		X	X	X	X	
Fecal Calprotectin (Quant-on-Cal kit)		X	X	X	X	X	X	X	X	X	
FBS / RBS									X	X	
T. Cholesterol		X	X	X	X	X	X	X	X	X	
LDL Cholesterol		X	X	X	X	X	X	X	X	X	
VLDL Cholesterol		X	X	X	X	X	X	X	X	X	
HDL Cholesterol		X	X	X	X	X	X	X	X	X	
Triglycerides		X	X	X	X	X	X	X	X	X	
Total Bilirubin		X	X	X	X	X	X	X	X	X	
Direct Bilirubin		X	X	X	X	X	X	X	X		
AST		X	X	X	X	X	X	X	X		
ALT		X	X	X	X	X	X	X	X		
ALP		X	X	X	X	X	X	X	X		
Total Proteins		X	X	X	X	X	X	X	X		
Albumin		X	X	X	X	X	X	X	X		
Blood Urea		X	X	X	X	X	X	X	X	X	
Serum Creatinine		X	X	X	X	X	X	X	X	X	
HBs Ag		X	X	X	X	X	X	X	X	X	X
Anti HCV		X	X	X	X	X	X	X	X	X	X
Stool for C. difficile toxin		X	X	X	X	X	X	X	X	X	X
CMV (histopathology and IHC)		X	X	X	X	X	X	X	X	X	X
Mantoux		X	X	X	X	X	X	X	X	X	X
X Ray Chest		X	X	X	X	X	X	X	X	X	X

Signature of Candidate **Signature of Supervisor**

Adverse Events											
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Week 2	Week 4	Week 8
Drug Hypersensitivity											
Herpes Zoster											
Tuberculosis											
Other Infections (Please specify)											
Venous Thromboembolism											
Cardiac Event (Please specify)											
Mood Changes											
Increased Appetite											
Fluid Retention											
Pathological Fractures											
Insomnia											
Acne											
Moon face											
Others (Please specify)											

Day	0	1	2	3	4	5	6	7	8	9	10	Week 2	Week 4	Week 8
Stool frequency during day														
Stool frequency during night														
Number of Stools With Blood														
Amount of blood in stools (Rate from 0-3) *0 means no blood and 3 means frank blood*														
Urgency of defecation (Rate from 0-2) *0 means no urgency and 2 means immediate*														
Stool Incontinence (Yes/No)														
General Well Being (Rate from 0-4) *0 means very good and 4 means terrible*														
EIMs														
SCCAI														

INFORMED PATIENT CONSENT

I.....D/o, W/o, S/o **"A PROSPECTIVE PLACEBO CONTROLLED RANDOMIZED CLINICAL STUDY OF TOFACITINIB AS AN ADJUNCT TO CORTICOSTEROIDS IN ACUTE SEVERE ULCERATIVE COLLITIS".** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____ निवासी _____ इस शोधकार्य **"A PROSPECTIVE PLACEBO CONTROLLED RANDOMIZED CLINICAL STUDY OF TOFACITINIB AS AN ADJUNCT TO CORTICOSTEROIDS IN ACUTE SEVERE ULCERATIVE COLLITIS"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"A PROSPECTIVE PLACEBO CONTROLLED RANDOMIZED CLINICAL STUDY OF TOFACITINIB AS AN ADJUNCT TO CORTICOSTEROIDS IN ACUTE SEVERE ULCERATIVE COLLITIS" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____
ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

_____
ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

_____
ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____
ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ